Develop New or Improved Methods for Diagnosing Disease and Disability

SCIENCE ADVANCES

$ Blood Test to Detect a Curable, Dangerous Cause of High Blood Pressure
$ Detection of Genes and Proteins from Lymphoma Cells Can Simplify the Diagnosis of Primary Intraocular Lymphoma
$ *In vivo* Imaging of Tumors in Mice with Protease-Activated Near-Infrared Fluorescent Probes
$ Patients with Mild Cognitive Impairment Can Be Clinically Characterized for Treatment Interventions
$ Hippocampal Volume MRI Predicts Conversion of Mild Cognitive Impairment to Alzheimer-s Disease
$ Genome-wide Search for Type 2 Diabetes Susceptibility Genes
$ Novel Brain Scanning Technique Detects Parkinson-like Condition
$ Dengue in Central America
$ Development of Guidelines for Cystic Fibrosis Carrier Genetic Screening
$ A Specific Indian AIDS Virus Strain
$ New Gene-Knockout Mice Reveal Role of Enzymes in Alcohol Metabolism
$ Scientists Trace Origins of Finns, an Informative Population for Genetics Studies
$ Chromosome 16 May Contain a Gene that Contributes to Alcoholism
$ BTGAPBThe Brain Tumor Genome Anatomy Project
$ Molecular Rescue Mission Unveils Genetic Link to Common Birth Defect
$ Mechanism of Action of Endocrine Tumor Formation
$ Identification and Characterization of Genes which Cause Hereditary Hearing Impairment
$ Genetic Associations in Age-Related Hearing Thresholds (Presbycusis)
$ Congenital Cytomegalovirus (CMV) Infection and Sensorineural Hearing Loss
$ Early Childhood Stuttering
$ Defining a Phenotype for Specific Language Impairment
$ Understanding the Causes of Hermansky-Pudlak Syndrome
$ Daylight Sets the Biological Clock through Photoreceptors Unrelated to Vision
$ Sleep Apnea in Early Childhood Is Associated With Asthma and Hypertension
$ Imaging Agent May Provide Information about Recovery after Revascularization
$ Why Do Some People Like Addictive Drugs?
$ Nerve Cell Growth And Development Studies Open Window To New Diagnostic Techniques
$ Association of Gene Polymorphisms, Tobacco Carcinogens and Lung Cancer
$ New Technology Provides Molecular Basis of Tuberculosis Pathogenesis and the Potential for Rational Design of New Vaccines and Diagnostics
$ Hypohidrotic Ectodermal Dysplasia
$ Teaching a Computer to Diagnose Airway Disease
$ Novel Imaging Technology for Joint Disorders
$ Early Identification of Hearing Impairment
$ A New Screening Tool for Lung Cancer
$ Magnetic Resonance Imaging of Cartilage May Aid Early Diagnosis, Treatment of Osteoarthritis
$ Hypothyroidism During Pregnancy Linked to Lower IQ for Child
$ Determining Accurate Placement of Feeding Tubes
$ Guidance for Treating Patients with Brain Aneurysms
$ Understanding the Causes of Preeclampsia
$ Biomolecular Underpinnings of Acute Human Leukemias

SCIENCE CAPSULES (page 419)

$ GJB2: A Major Cause of Hereditary Hearing Impairment in the United States
$ Epilepsy Caused by Pig Tapeworms
$ Improved Genetic Testing for Colorectal Cancer Risk
$ Biomarkers for Oxidative Stress Discovered
$ Psychiatric Disorders and Disability in Refugee Survivors of Mass Violence
$ Risk for Depression in Young Women during Transition to Adulthood
$ The Cumulative Toll of Trauma on Mental Health
$ Flow Cytometry Enables Rapid Genome "Fingerprinting"

STORIES OF DISCOVERY (page 423)

$ Osteogenesis ImperfectaBBrittle Bone Disease
$ Hereditary Hearing Impairment: Gene Discovery and Issues for Clinical Application
$ Turning Blue Babies Pink
$ A New Form of Type 2 Gaucher Disease

Blood Test to Detect a Curable, Dangerous Cause of High Blood Pressure

Background: Persistent high blood pressure (hypertension) has many possible causes. Rarely, hypertension results from a benign tumor of the adrenal gland, a key gland that sits atop each kidney. The tumor releases potent chemicals such as adrenaline into the bloodstream. Although rare, these tumors, called pheochromocytomas (Apheos@) are important in clinical medicine. Surgical removal of a pheo can cure the hypertension. Moreover, an untreated pheo, in response to seemingly mild stress, can secrete chemicals that produce catastrophic consequences such as heart attack and sudden death. Findings such as episodic severe hypertension, sweating, pallor, or headache may suggest to a physician that a pheo is present, but blood tests are not sensitive enough to detect pheos in all patients. This is especially a problem in patients with von Hippel-Lindau disease or multiple endocrine neoplasia type II, who inherit a predisposition to develop a pheo.

Advance: Researchers have now developed an effective blood test to detect pheos based on the detection of two chemicals produced at high levels by an enzyme present in the tumors.

Implications: The ability to identify or exclude a pheo should greatly increase the efficiency and decrease the cost of diagnostic evaluation of patients with high blood pressure and findings that suggest a pheo. Since identified gene mutations underlie von Hippel-Lindau disease or multiple endocrine neoplasia type 2, studying these disorders should lead to better understanding of how pheos develop and perhaps lead to new and improved methods for treatment and diagnosis.

Eisenhoffer G, Lenders JMW, Linehan WM, Waltther MM, Goldstein DS, and Keiser HR: Plasma normetanephrine and metanephrine for detecting pheochromocytoma in von Hippel-Lindau disease and multiple endocrine neoplasia type 2: NEJM 340:1872-79, 1999.

Detection of Genes and Proteins from Lymphoma Cells Can Simplify the Diagnosis of Primary Intraocular Lymphoma

Background: Primary central nervous system lymphoma (PCNSL) is a lymphoma that arises within the brain, spinal cord, and the eye. When PCNSL only involves the eye, it is called primary intraocular lymphoma. In the past 15 years, the incidence of the tumor has tripled. PCNSL is an aggressive cancer with a 5-year mortality of greater than 67%. Early diagnosis and prompt treatment may improve survival. Because appropriate treatment of PCNSL often involves radiation therapy and/or chemotherapy, a pathologic diagnosis is required. The diagnosis of this tumor is often difficult, and therefore an important goal for investigators is to find new methods to more easily diagnose this devastating disease.

Advance: After two decades of work scientists have now identified genes and proteins which are altered in the tumor cells of PCNSL. This discovery was a cooperative effort of an international team of scientists. Looking through a microscope, a scientist can remove tumor cells from the eye to look for the altered genes. This technique, called microdissection, combined with gene analysis is a powerful tool for study and diagnosis of cancer. By measuring cytokines, which are proteins that stimulate or inhibit immune cells, scientists have found high levels of certain cytokines in eyes with primary intraocular lymphoma. Consequently, this test has become a helpful adjunct in the diagnosis of intraocular lymphoma. Researchers have also found a possible link between herpes virus and this lymphoma, particularly in patients with AIDS. The detection of gene alternations and elevation of certain cytokines in PCNSL simplifies the diagnosis and allows patients to receive an earlier and more adequate therapy.

Implications: Altered regulation of cytokine production in lymphoma cells will allow a more precise diagnosis of the disease, leading to earlier detection and treatment. Learning how the altered genes function in lymphoma cells may provide information that will contribute to the understanding of tumor development and new strategies for effective cancer treatment.

Chan CC, Shen DF, Whitcup SM, Nussenblatt RB, LeHoang P, Roberge FG, Cassoux N, Herbort C, Zhuang Z: Detection of human herpesvirus-8 and Epstein-Barr virus DNA in primary intraocular lymphomas. Blood 93:2749-2751, 1999.

de Smet MD, Vancs VS, Kohler D, Solomon D, Chan CC: Intravitreal chemotherapy for the treatment of recurrent intraocular lymphoma. Br J Ophthalmol 83:448-451, 1999.

Buggage RR, Velez G, Myers-Powell B, Shen DF, Whitcup SM, Chan CC: Primary intraocular lymphoma with a low interleukin-10 to interleukin-6 ratio and intraclonal IgH sequence heterogeneity. Arch Ophthalmol 117:1239-1242, 1999.

In vivo Imaging of Tumors in Mice with Protease-Activated Near-Infrared Fluorescent Probes

Background: Early detection of small tumors is a mainstay of successful cancer treatment; cancers detected early, before they have had the chance to spread, are more easily treatable and more frequently curable than more advanced cancers. However, current methods for the non-invasive detection of small tumors are limited in their ability to distinguish small areas of abnormal cells from larger surrounding areas of normal tissue.

Advance: NIH grantees have developed a new method to more precisely image tumor cells. They injected tumor-bearing mice with a unique imaging agent composed of near-infrared fluorescence imaging probes (NIRF probes) coupled with a novel substance that moves efficiently into tumor cells. When the agent was internalized into the cancer cells, enzymes within that cell Aactivated@ the agent and caused it to fluoresce. The fluorescence could then be detected non-invasively. The agent was not activated in non-tumor cells. Using this technique, the investigators were able to image tumors smaller than 300 microns (three-tenths of a millimeter) in diameter.

Implications: Although this new technique is in the early stages of development, and has yet to be tested in the clinic, it shows great promise for the non-invasive detection of very small tumors. Secondary Performance area: Develop new or improved instruments and technologies for use in research and medicine.

Weisslander R, Tung C-H, Mahmood U, and Bogdanov A: *In vivo* imaging of tumors with protease-activated near-infrared fluorescent probes. Nature Biotechnology 17: 375-378, 1999.

Patients with Mild Cognitive Impairment Can Be Clinically Characterized for Treatment Interventions

Background: Individuals with mild cognitive impairment (MCI) have a memory impairment beyond that expected for age and education, yet they are not demented. These people are becoming the focus of observational and early intervention trials aimed at preventing the development of Alzheimer=s disease (AD). A prospective, longitudinal study in the setting of a general community clinic was carried out to clinically characterize subjects with MCI, both cross-sectionally and longitudinally.

Advance: This study found that individuals with mild cognitive impairment differed from normal controls primarily in the area of memory, with other cognitive functions being comparable. Compared to very mild AD patients, the memory of MCI individuals was similar, but AD patients were impaired in other cognitive domains. The study concluded that MCI can be characterized as a clinical entity, and documented the clinical course of MCI individuals with respect to change on standardized tests and diagnostic outcome. Longitudinal performance demonstrated that the subjects with MCI declined at a rate greater than that of the controls but less rapidly than the patients with mild AD. The results also demonstrated that people with MCI are at increased risk of progressing to AD.

Implications: Individuals who meet the criteria for MCI can be differentiated from normal control subjects and those with very mild AD. This MCI group appears to constitute a clinical entity that can be characterized for treatment interventions because they are at increased risk of progressing to AD. Each year, 15-20% of MCI individuals convert to AD versus 1-2% of people in the general population over 65. These results are the basis of the ongoing NIA-supported Memory Impairment Study, carried out by the Alzheimer=s Disease Cooperative Study, to determine whether Vitamin E or Aricept can delay or prevent the onset of AD in people with MCI. A number of pharmaceutical companies have also initiated MCI trials to test other drugs. If this type of secondary prevention study does turn out to be a useful and practical way of assessing drug interventions, which have the potential for delaying the onset of or entirely preventing AD, then it will be possible to test, in a cost-efficient way, many more compounds than would be possible in primary prevention studies. [secondary B prevention]

Peterson RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, and Kokmen E: Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56: 303-08, 1999.

Hippocampal Volume MRI Predicts Conversion of Mild Cognitive Impairment to Alzheimer=s Disease

Background: The transition from a normal cognitive state to clinically recognized Alzheimer=s disease (AD) occurs gradually over many years. Memory impairment is usually the initial manifestation of dementia in AD. Because of the gradual transition from normal cognition to AD, however, clinicians are presented with the diagnostic problem of determining whether evidence of mild memory impairment in an older individual represents the earliest manifestation of AD or is a more benign forgetfulness that may not progress to dementia. The clinical criteria for classification of patients with mild cognitive impairment (MCI) have been established, and it has been found that these individuals convert to AD at a substantially greater rate than that of the general population over 65. Structural and functional imaging has been shown to be of use as diagnostic markers of AD, but most imaging studies have been cross-sectional and have been designed to demonstrate differences between older controls and patients who were already demented.

Advance: MRI volumetric imaging studies were conducted on patients with a clinical diagnosis of mild cognitive impairment. These patients were then followed up annually with clinical and cognitive assessments for approximately three years. The study focused on volume measurement of the hippocampus because this brain structure plays a central role in memory function and is the site of the earliest tangle pathology in AD. In older individuals with MCI, hippocampal atrophy at baseline was predictive of an increased risk of subsequent conversion to AD; that is, the smaller the hippocampus, the greater the risk.

Implications: Unlike genetic markers, which are present at birth, imaging studies can actually identify development of the disease itself. This is true for both structural imaging measures and functional measures such as positron emission tomography, because imaging studies become abnormal only when the disease process itself has produced deviation from normal cerebral function or anatomy but before clinical diagnosis. Ideally, the imaging finding should represent markers of incipient disease. The present data do suggest that MRI-based volume measurement of the hippocampus fulfills this criterion. Thus, it is possible to identify people who are beginning to develop the brain structural changes of the disease prior to the ability to make the clinical diagnosis of AD. Given this diagnostic ability to detect early disease, it will be important to develop treatments which can stop the brain changes before clinical deterioration sets in. [secondary B treatment]

Jack CR, Jr., Petersen RC, XU YC, O=Brien PC, Smith GE, Ivnik RJ, Boeve BF, Waring SC, Tangalos EG, and Kokmen E: Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 52: 1397-403, 1999.

Genome-wide Search for Type 2 Diabetes Susceptibility Genes

Background: Diabetes mellitus affects an estimated 16 million people in the United States and costs the nation about $105 billion annually in health-related expenditures. Type 2 diabetes, the noninsulin-dependent form of the disease, is believed to result from a complex interplay between genetic and environmental factors. Although several genes have been identified that may increase the risk of type 2 diabetes, these genes appear to be relevant only to unusual forms of the disease in a few families and are not important contributors to the more typical condition.

Advance: By studying DNA samples from 42 multigenerational families, each of which had at least two siblings who manifested type 2 diabetes before age 65, scientists have identified a novel diabetes susceptibility locus on chromosome 1 in a region with many transcribed genes, including genes that control free fatty acid levels and glucose metabolism. More than 600 affected and unaffected family members were assessed for this study at the University of Utah. The data indicated that nonaffected siblings who harbor this newly identified susceptibility locus are 2.8 times more likely to develop diabetes.

Implications: Identifying the genes that contribute to type 2 diabetes will help researchers to uncover the molecular basis of this disorder, which in turn may lead to improved treatment strategies. Discovery of the underlying genes may also enable early identification of at-risk individuals, who might delay or prevent the onset of disease by making certain lifestyle changes such as exercising more or watching their diet.

Elbein SC, Hoffman MD, Teng K, Leppert MF, Hasstedt SJ: A genome-wide search for type 2 diabetes susceptibility genes in Utah Caucasians. Diabetes 48:1175-82, 1999.

Novel Brain Scanning Technique Detects Parkinson-like Condition

Background: With the graying of the nation's population, neurodegenerative diseases have become much more prevalent. Parkinson's disease, one of the most common neurological disorders, affects about 1 million Americans. At the cellular level, Parkinson's disease is characterized by severe depletion of neurons that release the neurotransmitter dopamine, which is needed for normal movement and muscle control. By developing techniques to detect early loss of such neurons, scientists hope to enable timely intervention that will prevent further deterioration or even restore lost neurons through use of embryonic system cells.

Advance: By studying a nonhuman primate model for Parkinson's disease, investigators have developed and evaluated an imaging technique that enables detection of dopamine-specific neurons. Developing radioactively labeled drugs that selectively identify dopamine-secreting neurons has been a major challenge. The investigators discovered that progressive dopaminergic fiber loss can be discerned by positron emission tomography (PET scans) using specific chemicals to label dopamine reuptake sites. The findings will allow scientists to mathematically model progressive degeneration of dopamine terminals, determine the rate of degeneration, and predict when signs of the disease will likely appear, which would be a valuable diagnostic tool.

Implications: An estimated 40,000 new patients in the United States are diagnosed with Parkinson's disease every year. The development of "designer drugs" that target and enable detection of affected neurons may also allow early treatment of the disease. Drugs that target specific neurons can also be used as vehicles to carry prospective therapeutic agents to affected neurons. [secondary B treatment]

Brownell AL, Jenkins BG, Isacson O: Dopamine imaging markers and predictive mathematical models for progressive degeneration in Parkinson=s disease. Biomed & Pharmacother 53:131-40, 1999.

Dengue in Central America

Background: Dengue fever and its most severe form, dengue hemorrhagic fever/dengue shock syndrome, are considered among the most important and widespread reemerging infectious diseases in developing countries. While poorly understood, dengue virus is one of a number of insect-borne diseases that cause death and disease around the world. Simple, fast and accurate characterization of these diseases is an important step in ultimately finding a cure.

Advance: Existing methods for characterizing viruses are costly and complicated to do, particularly in developing countries with limited capabilities and resources. Researchers in California and Central America have developed a new technique using a PCR-based subtyping method known as restriction site-specific PCR to rapidly and accurately define the virus responsible for dengue in Central America. This technique is a simple, one-step process using widely available chemicals and can be done in the country where the disease is found. Using this new information, the researchers were able to track the movement of the dengue virus from Asia and Africa to the Americas.

Implication: Characterizing viruses by means of genetic analysis reveals important information about the spread of disease over time and geography. Using this information, physicians and scientists can identify risk factors and predict the severity of disease. Modern genetic techniques, particularly in developing countries, is greatly enhancing our understanding of new and reemerging diseases, providing our health care establishment with accurate and reliable information, more rapidly and at lower cost.

Harris E, Sandova E, Xet-Mull AM, Johnson M, and Riley LW. Rapid Subtyping of dengue viruses by restriction site-specific (RSS) B PCR. Virology 253: 86-95,1999

Development of Guidelines for Cystic Fibrosis Carrier Genetic Screening

Background: Cystic fibrosis (CF) is one of the most common inherited disorders in Caucasians. It is estimated that 1 in 25 Americans of European ancestry are CF carriers, i.e., they have a single copy of an altered gene linked to the development of CF. Because CF is a recessive disorder, individuals with only a single copy of the altered gene are not affected by CF. However, due to the relatively high prevalence of CF carriers, 1 in 2500 individuals will inherit two copies of the altered gene and be affected with CF. When the first genetic tests for this disorder became available, it was determined that, given the limitations of the test, it should be offered only to those individuals who had a family history of CF. However, health professional groups and others soon became concerned that, as genetic testing technologies improved, there would be increasing pressure to offer genetic screening for disorders such as CF to a much wider population. Of particular concern were issues such as whether people would be able to understand complex genetic test results when they had no experience with and little knowledge of the disease, genetics, and genetic testing; how people would respond to an imperfect test; and whether these tests could lead to more anxiety and uncertainty than they relieved. There was particular concern that these issues would be exacerbated in diverse communities, in which the test performed even less well.

To address these issues and to begin to define the best methods for educating and counseling individuals who might desire CF genetic testing, the NIH funded eight studies in 1991. From 1992-1997, more than 35 papers detailing their research findings were published in peer-reviewed journals.

In April 1997, a NIH Consensus Development Conference looking at Genetic Testing for Cystic Fibrosis examined the data from these and other studies and heard presentations from a number of experts in the field. The independent, non-federal consensus recommended that the offering of CF genetic testing be expanded to include all individuals planning a pregnancy. The panel acknowledged that implementation of their recommendations would be complex and would mark the first time that offering testing for a specific genetic disorder would become the standard of care for a general population. As a result, they concluded "It is essential that the offering of CF carrier testing be phased in over a period of time in order to ensure that adequate education and appropriate genetic testing and counseling services are available to all persons being tested."

Advance: To ensure that these recommendations were implemented in a safe and effective manner, the NIH is supporting the American College of Obstetricians and Gynecologists and the American College of Medical Geneticists to develop clinical, laboratory and educational guidelines. In 1998, a steering committee and three working groups were formed with representation from a number of professional and consumer organizations. The clinical practice working group is developing practice guidelines for health care providers who will have the primary responsibility for offering these tests. The laboratory standards working group is developing recommendations about what mutations should be included in the testing panel. The education and informed consent working group has developed and is currently pilot testing educational and informed consent materials to be used by health professionals. All of the guidelines and materials are expected to be available for general distribution in the spring of 2000.

Implications: As increasing numbers of genes associated with a wide range of illnesses are discovered, more and more health care professionals are being asked to provide genetic testing services. However, many still do not have the experience to adequately educate and counsel large numbers of patients about genetic testing. The multi-disciplinary effort to develop professional and laboratory practices and educational and informed consent materials to govern the use of the CF test in a general population is an important model for the introduction of future genetic testing services. [secondary B treatment]

A listing of the principal investigators is available online at:
http://www.nhgri.nih.gov:80/About_NHGRI/Der/Elsi/elsiabs.html#Clinical

The publications that resulted from each of these studies are listed online by the name of the principal investigator at:
http://www.nhgri.nih.gov:80/About_NHGRI/Der/Elsi/elsipub.html

Love CB, and Thomson EJ: Genetic testing for cystic fibrosis: January 1989 through February 1997. Current Bibliographies in Medicine *97-2*. Bethesda, Maryland: National Library of Medicine, March 1997. 78p. Available online at: http://www.nlm.nih.gov/pubs/cbm/cystic_fibrosis.html

Genetic Testing for Cystic Fibrosis. April 14-16, 1997. NIH Consensus Development Conference Program and Abstracts Book. Available online at: : http://odp.od.nih.gov/consensus/cons/106/106_intro.htm

Genetic Testing for Cystic Fibrosis. NIH Consensus Statement 1997. April 14-16;15(4):1-37. Available online at: http://odp.od.nih.gov/consensus/cons/106/106_intro.htm

Mennuti MT, Thomson E, and Press N: Screening for cystic fibrosis carrier state. Obstetrics & Gynecology: 93(3); 456-461, 1999.

Mennuti MT: Offering CF carrier screening: Who set the goal, and what is the goal? Genetics in Medicine 1:125-6, 1999.

A Specific Indian AIDS Virus Strain

Background: According to World Health Organization estimates, India will have the greatest number of AIDS virus infected people worldwide by the end of this decade. Anti-viral drugs, generally available in developed nations that can extend the duration and improve the quality of life generally are not available in developing countries because of prohibitive costs. The most cost-effective strategy for the global control of the AIDS epidemic would be a safe, effective and affordable vaccine. Development and effective use of a vaccine against the AIDS virus, however, will require knowledge of the viral strains circulating within the target population. Prior to this study, little was known about the diversity of AIDS virus strains in India.

Advance: This landmark study represents the first characterization of the complete genetic code of a AIDS virus strain isolated from infected patients in India. The genetic code of the virus isolated from one patient appeared to be a hybrid of two previously known strains. Characteristics of the AIDS virus which are known to be targets of the body=s immune defenses were substantially different in the strains isolated in India compared to the strain most prevalent in the U.S.

Implications: The data describing different strains of the AIDS virus gathered from scientists all over the world is growing exponentially but is not yet representative of the global distribution of the disease. Some strains have been reported in nearly every region affected by AIDS and other strains predominate in different countries. The data obtained for the AIDS virus strains from India is likely to further facilitate vaccine development efforts in India by providing more accurate information than currently available data from other parts of the world. The information gleaned from the data will design AIDS vaccine candidates as well as measure an immunized person=s response to the vaccine.

Lole KS, Bollinger RC, Paranjape RS, Gadkari D, Kulkarni SS, Novak NG, Ingersoll R, Sheppard HW and Ray SC: Full-Length Human Immunodeficiency Virus Type 1 Genomes from Subtype C-Infected Seroconverters in India, with Evidence of Intersubtype. Journal of Virology 73: 152-160, 1999

New Gene-Knockout Mice Reveal Role of Enzymes in Alcohol Metabolism

Background: Enzymes are proteins that initiate and speed up chemical reactions throughout the body. For example, enzymes are involved in metabolismBprocessing substances into components that the body can use or excrete. Alcohol dehydrogenase (ADH) is the first in a series of enzymes that metabolize alcohol. Differences in alcohol metabolism may influence the rate at which people eliminate alcohol from their system and, thus, their tolerance for drinking and risk for alcoholism.

ADH occurs in many formsBAisozymes@Bcalled Adh1, Adh2, etc. The function of each is not yet clear. Scientists now are studying these isozymes with gene-knockout techniques; that is, inactivation of a gene. The way genes relate to enzymes is that each gene Ainstructs@ cells on how to make a specific protein, such as ADH. When scientists identify the gene involved in producing a protein, they can alter that gene in animals. Altering the gene alters the protein it produces, and researchers can observe how these changes affect the animals= response to alcohol.

Studying the influence of various factors on alcohol=s effects is difficult. There are so many of these factors, from the genetic and molecular levels to the behavioral level, that it is hard to separate the influence of one from the others. Gene knockouts allow scientists to isolate the effects of single genes on biological or behavioral responses to alcohol, clearing the picture considerably.

Advance: Researchers created separate groups of mice deficient in Adh1, Adh3, or Adh4 via gene knockouts. The researchers injected alcohol into these animals and into a genetically unaltered comparison group. Mice deficient in Adh1 and, to a lesser extent, Adh4, cleared alcohol from their bodies significantly more slowly than did Adh3-knockout mice and comparison mice.

In a separate metabolism-related experiment, researchers found that Adh4 (and, to a lesser extent, Adh1), but not Adh3, knockout mice injected with vitamin A substantially reduced their production of retinoic acid, the final product of vitamin A metabolism. Retinoic acid plays a major role in development of the brain and other organs damaged in fetal alcohol syndrome.

Implications: These findings could lead to methods of identifying biological variations that put people at risk of alcoholism. In addition, the fact that mice without Adh4 and, to a lesser extent, Adh1, are less able to convert vitamin A to retinoic acid suggests that these isozymes are needed for production of this important developmental substance. Alcohol interferes with metabolism of vitamin A to retinoic acid. Scientists are investigating whether this interference contributes to fetal alcohol syndrome in the offspring of women who drink during pregnancy. [secondary B prevention]

Deltour L, Foglio MH, Duester G: Metabolic Deficiencies in Alcohol Deyhdrogenase Adh1, Adh3, Adh4 Null Mutant Mice. Journal of Biological Chemistry, 274(24):16796-16801, June 1999.

Scientists Trace Origins of Finns, an Informative Population for Genetics Studies

Background: When scientists look for genes that cause diseases, what they really are looking for are gene variants. If they find that a particular gene variant and disease tend to be simultaneously present—that is, statistically linked—in a population, that gene variant is implicated in the disease. People with different variants of the gene have different odds for getting the illness.

The search for disease-influencing variants is simplified when scientists study isolated populations, because their people are more likely to be genetically similar than are those of other, mixed populations. The effects of mutations on disease stand out more under these conditions, making them easier to identify. Alcohol researchers are among the geneticists who study the people of Finland, because they are thought to represent such a population. The thinking has been that Finns originated from a single group of founders, remained relatively isolated, and recently expanded rapidly.

However, new DNA evidence suggests that Finns had two major groups of founders. Alcohol researchers recently examined this assertion. Scientists can trace the lineage of a population through DNA studies and statistical analyses that determine the chronological order in which variations of genes occurred. However, many factors can confuse the picture of a population=s genetic history. For example, migrating members of other populations can introduce gene mutations into the original population. The reshuffling and exchanging of genetic material that occurs during reproduction is another confounding factor.

In the study described here, scientists eliminated some of these confusing factors by studying the gene variants of the Y chromosome (present only in males), because it differs from other chromosomes in important ways. It contains few genes; the genes it contains are passed only from fathers to sons; and, most important, the largest part of the Y chromosome (the part studied here) does not engage in the reshuffling and exchange of genes that other chromosomes undergo as part of reproduction. Unlike with other chromosomes, scientists can study the inheritance of the Y chromosome in its entirety. These unique features obviate some of the variables that otherwise would confuse the picture. The researchers studied haplotypes, sets of variants of linked genes on the Y chromosome that are passed to offspring as units.

Finding: Researchers found dramatic differences in variation on the Y chromosome, revealing two sources of origin in the Finnish population. They also identified a subgroup of Finns who are descended from one of the country=s founding groups and whose genetic similarity is conducive to genetic studies. Scientists also found that a gene variant on the Y chromosome may make a minor contribution to risk for alcoholism in Finnish males.

Implications: The subgroup of aboriginal Finns identified in this study will provide researchers with a clearer genetic backdrop on which to conduct studies linking gene variants to diseases. Identifying these gene variants will raise new diagnostic and treatment possibilities.

Kittles R, Perola M, Peltonen L, Bergen AW, Aragon RA, Virkkunen M, Linnoila M, Goldman D, Long JC. Dual Origins of Finns Revealed by Y Chromosome Haplotype Variation. American Journal of Human Genetics, 62:1171-1179, 1998.

Chromosome 16 May Contain a Gene that Contributes to Alcoholism

Background: Since genes account for about half of the risk for alcoholism, identifying the genes involved is of paramount importance. However, this is a complex proposition. Multiple genes influence the disease in any given individual, and the proteins these genes produce engage in a diverse array of intricate biological mechanisms that influence alcoholism. Scientists sometimes can track down a gene involved in alcoholism by observing how the protein it produces affects these mechanisms.

Compounding these factors enormously is this: Alcoholism is influenced by different genes in different people. As a result, there are many subtypes of alcoholism (even though they have similar outcomes), depending on the genes involved and on the biological mechanisms driven by these genes. People whose alcohol-related behavior is regulated by the same biological mechanisms are likely to have the same genes at work, and identifying groups of people who share the same manifestations of alcoholism simplifies the genetic search. Thus, an important and difficult task for geneticists is to establish classes of alcoholics with similar profiles.

Another component of the search for genes that influence alcoholism involves finding their locations on chromosomes. Researchers have developed methods of identifying the chromosomal region on which a gene resides. Described below is one method called Alinkage.@

Scientists have created a map of the body=s 23 chromosomes, each of which contains hundreds of genes that affect different traits and are passed onto offspring. Finding the location of the gene or genes that influence specific traitsBpropensity for drinking, for exampleBis a major challenge for genetics researchers. Locations of some genes already have been identified and have been marked on the chromosomal map; they are called Amarkers.@ Genes can appear in various forms called Aalleles,@ and the form that an allele takes is manifested in a person=s traits. Genes near each other on a chromosome are likely to be passed onto offspring in tandem. Scientists studying a trait influenced by a gene whose location is unknown can perform statistical analyses that reveal whether both that trait and a known marker gene appear in individuals more often than would occur by chance. If so, it is likely that the gene governing the trait under study is in the same chromosomal region as the marker gene.

Advance: Researchers used latent class analysis, a statistical method, to identify a group of alcoholics with a more similar symptom profile than would have been attainable from a group classified by standard clinical definitions of alcoholism. Via linkage analysis, the researchers found that a region of chromosome 16 may contain a gene that affects alcoholism in this group.

Implications: As researchers identify alcoholics who share the same symptom profiles, they simplify their search for genes that influence alcoholism. Identifying these genes will help scientists track alcohol-related biological mechanisms. Eventually, scientists can use their results to consider designs for interventions intended to therapeutically alter these mechanisms in specific classes of alcoholics.

Foroud T, et al.: Linkage of an Alcoholism-Related Severity Phenotype to Chromosome 16. Alcoholism: Clinical and Experimental Research, 22(9):2035-2042, December 1998.

BTGAPBThe Brain Tumor Genome Anatomy Project

Background: About 160,000 Americans suffer from brain tumors, and each year more than 40,000 new cases are diagnosed. Difficulties in accessing the brain, notably the blood brain-barrier which excludes many drugs, present special challenges for treatment, and currently available treatmentsBsurgery, radiation and chemotherapyBcan themselves have damaging consequences and are largely ineffective against many brain tumors.

Decades of research have taught us that brain tumors, like all forms of cancer, are in a real sense genetic disorders. While most tumors are not inherited, all tumors reflect mutations or improper activation of genes that control the function of cells. For this reason, National Institute of Neurological Disorders and Stroke , in collaboration with the National Cancer Institute=s Cancer Genome Anatomy Project (CGAP), has embarked on an ambitious Brain Tumor Genome Anatomy Project (BTGAP). BTGAP is developing a comprehensive molecular profile of primary brain tumors at progressive levels of malignancy. Understanding brain tumors at the molecular levelBat the level of the genes and proteins that control cell functionBis the key to developing effective therapies.

Advance: The first phase of BTGAP aims to determine which genes are active in the most prevalent adult and childhood brain tumors. Work began by focusing on the genes that are active in gliomas. Gliomas arise from glia, the supporting cells of the nervous system, and are the most serious and prevalent form of primary brain tumor because they migrate and destructively infiltrate adjacent areas of the normal brain, presenting special challenges for treatment. These initial studies have revealed that studying brain tumors is a surprisingly rich path for the discovery of new genes. Already well over 1000 unique genes have been detected, and the number is still climbing, which makes BTGAP not only an extraordinarily productive source of new information about brain tumors but also one of the richest of all sources for revealing human genes. The information and resources being developedBincluding cDNA libraries, clones, and sequence dataBis being made accessible to all scientists through the CGAP database infrastructure to help catalyze progress as rapidly as possible.

Implication: Future phases of BTGAP will compile molecular profiles of more tumor types in adults and children, apply advanced technologies such as laser capture microdissection to focus on single cell types, use array technologies to look at thousands of genes and proteins simultaneously, and leverage the molecular findings to unravel the basic mechanisms of glial and glioma cell proliferation, migration, and specialization. The ultimate goal of BTGAP is to use the new genetic information to understand how tumor cells arise and to develop effective ways to prevent, diagnose, or treat tumors of the nervous system. Finding better ways to diagnose tumors, discovering unique tags to target drugs to cancer cells, evaluating which therapies might work for a particular patient=s tumor, and learning how to inactivate the destructive invasiveness of tumor cells are just a few examples of how molecular understanding may help combat brain tumors.

http://www.ncbi.nlm.nih.gov/ncicgap/cgaplb.cgi

Molecular Rescue Mission Unveils Genetic Link to Common Birth Defect

Background: One of every 200 babies is born with a disorder called hydroureteronephrosis, one of a spectrum of urinary tract problems that are the most common survivable inherited birth defects in humans. The condition is essentially a physiological plumbing problem in which urine cannot make its way to the bladder. This occurs because of an anatomical defect in the tubes (ureters) that connect the kidneys to the bladder, and is often diagnosed by prenatal ultrasound screening. In many cases, hydroureteronephrosis can be surgically repaired, but scientists continue to seek the underlying cause of the problem.

Advance: Researchers have uncovered at least one genetic cause for hydroureteronephrosis. The finding links a previously studied gene, called GATA-2, with ensuring the proper development of the genitourinary tract. From earlier work, scientists already knew that GATA-2 is critical for the formation of blood. But until now, no one suspected that GATA-2 did anything besides helping the developing organism make blood. When researchers first created mice that lacked the GATA-2 gene, the inability of the mutant mice to make blood caused them to die before birth. Using a new genetic technique that involves cutting and pasting enormous chunks of DNA into the chromosomes of mice, scientists have for the first time succeeded in rescuing mutant GATA-2-less mice from death. This technical feat revealed GATA-2's second, but equally important, function in programming the correct development of the kidney and bladder.

Implications: The discovery paves the way for researchers to identify diagnostic and/or treatment strategies to combat a variety of bladder and kidney disorders in newborns, including hydroureteronephrosis. But while the disease-related implications of the finding may be readily apparent, researchers are equally excited about the more general, but profound, impact the discovery will have on the larger task of ascribing genes to functions in the developing mouseBand almost certainly humanBembryo. The molecular strategy used to uncover GATA-2's unknown function should prove to be a very powerful tactic to identify the more subtle genetic abnormalities that lead to disease.

Zhou Y, Lim K-C, Onodera K, Takahashi S, Ohta J, Minegishi N, Tsai F-Y, Orkin SH, Yamamoto M, and Engel JD: Rescue of the embryonic lethal hematopoietic defect reveals a critical role for GATA-2 in urogenital development. EMBO Journal 17:6689-700, 1999.

Mechanism of Action of Endocrine Tumor Formation

Background: Inherited cancers are of great scientific interest, in part because of their potential to lend insight into the general mechanism of carcinogenesis. In most inherited cancers the genes responsible are of the tumor suppressor type. An affected individual usually inherits one altered or bad copy of the responsible gene from an affected parent, but the tumors have lost the second copy of the good gene through a cell mutation event. The importance of the gene discovery often extends beyond affected families, as the same gene often plays a role in sporadic tumors. In these cases, somatic mutations have occurred in both good genes. NIH researchers have been studying multiple endocrine neoplasia-type 1 (MEN1) for a number of years. MEN1 is an inherited cancer syndrome that can cause multiple benign tumors of the parathyroid and pituitary glands, as well as islet cell tumors leading to pancreatic cancer. A unique collaboration between NIH and academia recently led to the discovery of the gene for MEN1, an important goal of the neuroendocrine tumor research community. NIH researchers have found that the MEN1 gene is expressed throughout the body, not just in the endocrine glands as would have been predicted based on tumor characteristics. They have also shown that mutations of the MEN1 gene contribute to a large fraction of both inherited and sporadic neuroendocrine tumors. These findings suggest that MEN1 is a tumor suppressor gene, yet it is very different from any of the known tumor suppressors. Investigators now hope to learn from MEN1 and its protein product, menin, how endocrine tumors and cancers grow.

Advance: NIH intramural researchers have shown that the protein menin is found in the cell nucleus, indicating a potential role of this protein as a transcription factor. Transcription factors are proteins responsible for regulating gene activation (expression) and controlling cell growth. To ascertain the molecular function of menin, researchers attempted to identify menin-interacting proteins using a yeast system in which menin served as the Abait@. They identified the transcription factor JunD as a direct menin-interacting partner. Most recently, they have shown that menin binds to and inhibits JunD, confirming its role as a transcription factor and opening up a pathway that has never before been implicated in the origin of hereditary tumors.

Implication: As a result of these discoveries, physicians will soon be able to screen families at risk for MEN1 more easily. The application of molecular genetic, cell biologic, and animal model approaches can now be initiated to gain an understanding of the molecular basis of this disorder. The use of animal models in which the MEN1 gene is deleted could help place the gene in pathways occupied by other known genes and could help identify steps within a pathway by which normal cells are transformed into cancerous cells. Activation or inactivation of the gene could be used as a diagnostic tool in the management of cancer. The discovery of the gene also provides a target for the design of drugs to prevent or treat benign and malignant tumors. [secondary B treatment]

Agarwal SK, Guru SC, Heppner C, Erdos MR, Collins RM, Park SY, Saggar S, Chandrasekharappa SC, Collins FS, Spiegel AM, Marx SJ, and Burns AL, *Menin interacts with the AP1 transcription factor JunD and represses JunD-activated transcription*. Cell 1999;96:143-52.

Identification and Characterization of Genes which Cause Hereditary Hearing Impairment

Background: Roughly one child in a thousand is born with hearing impairment that compromises the development of normal spoken language skills. In about one half of these children, the underlying cause is a mutation in a gene whose function is essential for normal auditory function. By understanding the identity and function of these genes and their associated gene products, scientists and physicians can be more timely and precise in the diagnosis of hereditary hearing impairment, and provide the optimal intervention strategy for each of these affected children as soon as possible, thereby maximizing the potential for developing language skills essential for human communication.

Advance: Within the last seven years, the location of over forty genes that cause hereditary hearing impairment has been determined. Within the last two years, ten of these genes have been cloned, and the nature of the mutations causing hereditary hearing impairment determined. These genes encode a remarkable array of proteins with different functions including: (1) gap junction proteins that allow small molecules to pass freely between cells in the inner ear; (2) potassium channels that are essential to maintain the unique electrochemical composition of inner ear fluids; (3) unconventional myosin proteins believed to shuttle molecular Acargo@ from one part of the cell to another; (4) proteins that make essential inner ear structures which are unique to the inner ear; and (5) proteins whose function is unknown. Scientists continue to clone additional hereditary hearing impairment genes, and to identify new mutations in genes already identified. The dizzying pace of this research is fueled by the spectacular success of the researchers in elucidating the structure and sequence of the human genome.

Implications: Identification of the genes where mutations cause hereditary hearing impairment will lead to timely and precise diagnosis, followed by early and more effective intervention strategies that will optimize the language skills of affected children. Moreover, it is likely that different forms of some of the same genes where mutations cause profound hereditary hearing impairment confer susceptibility to noise-induced hearing loss, or age related hearing loss (presbycusis) that is very common among older Americans. With the ability to predict who is at increased risk, strategies to minimize or delay hearing loss within the high-risk population can be developed. Finally, the identity of these genes provides hearing scientists hitherto unexpected knowledge of metabolic pathways and structures essential for normal auditory function.

Fransen E et al: High prevalence of symptoms of Meniere=s disease in three families with a mutation in the COCH gene. Human Molecular Genetics 8(8): 1425-1429, 1999.

Griffith AJ and Friedman TB: Making sense out of sound. Nature Genetics 21: 347-349, 1999.

Van Laer L et al: Nonsyndromic hearing impairment is associated with a mutation in DFNA5. Nature Genetics 20: 194-197, 1998.

Morell RJ et al: Mutations in the connexin 26 gene (GJB2) among Ashkenazi Jews with nonsyndromic recessive deafness. The New England Journal of Medicine 339(21): 1500-1505, 1998.

Genetic Associations in Age-Related Hearing Thresholds (Presbycusis)

Background: Age-related hearing loss is a condition that affects a growing segment of American society. Based largely on clinical observations it has been presumed for some time that age-related hearing loss or presbycusis may be inherited and that genetic factors may influence the rate and severity of hearing loss. However, the genetic factors that underlie presbycusis are unknown, and the nature and extent of presbycusis occurring in related individuals has not been well documented.

Advance: A recent study utilizing a large population of related and non-related individuals has demonstrated that a clear familial aggregation (genetic component) exists for age-related hearing loss. The investigators were able to demonstrate a genetic component by measuring several different hearing thresholds at specific frequencies that are most commonly affected in presbycusis. The estimates of a genetic component to age-related hearing loss were stronger than, or comparable to, those seen for blood pressure or cholesterol levels.

Implications: The finding of a substantial genetic basis for presbycusis provide a rationale for further molecular genetic linkage studies to locate the genes responsible for this trait. The identification and characterization of such genes would have implications for predicting who is at increased risk for presbycusis, and delaying the onset of age-related hearing loss. [secondary B prevention]

Gates GA et al: Genetic associations in age-related hearing thresholds. Arch Otolaryngol Head Neck Surg 125, June 1999.

Congenital Cytomegalovirus (CMV) Infection and Sensorineural Hearing Loss

Background: Congenital infection with cytomegalovirus (CMV) is a very common cause of hearing loss in infants and young children. NIH-supported scientists continue to make significant progress towards determining the effects of CMV on sensorineural hearing loss (SNHL), as well as understanding the mechanisms and epidemiology of CMV maternal transmission. Recent results demonstrate a highly significant effect of CMV infection on late-onset SNHL.

Advance: Investigators studying a cohort of 388 children identified as having congenital CMV infection at birth, performed repeated hearing evaluations to assess whether and when hearing loss occurred. While SNHL was detected in 5.2% of CMV-infected newborns, by 6 years of age the cumulative incidence of SNHL in this group was more than 15%. These results argue for a combined approach of universal screening of neonates for both hearing and for congenital CMV infection. CMV-infected children could then be tested regularly for the development of late-onset SNHL.

Implications: Additional studies are aimed at the characterization of maternal CMV status in an effort to determine the relationship between the type of maternal infection (recurrent, or primary) and congenital CMV infection. This research is critical for fully determining the natural history of maternal CMV infection and mother-to-child transmission that contribute to early- and late-onset SNHL. Such studies are essential for the development of rational clinical approaches aimed at ameliorating CMV-induced congenital hearing loss. [secondary B prevention]

Fowler KB et al: Newborn hearing screening: Will children with hearing loss caused by congenital cytomegalovirus infection be missed? Journal of Pediatrics 135(1): 60-64, 1999.

Boppana SB et al: Symptomatic congenital cytomegalovirus infection in infants born to mothers with preexisting immunity to cytomegalovirus, Pediatrics 104(1): 55-60, 1999.

Early Childhood Stuttering

Background: Stuttering is a disorder that typically begins between ages 2 and 5, afflicting approximately 5% of preschool children. When it persists, the disorder causes serious impairment in verbal communication that is often associated with significant emotional and social adjustment difficulties. Academic achievements and future career opportunities may also be compromised. For many years, most research on this disorder focused on adults who stutter. However, during the past few years NIH has also played a major role in supporting research projects that deal with very young children at the stage when the disorder begins. A large-scale longitudinal investigation of children who stutter is examining various aspects of the stuttering as it persists or subsides during the course of several years. Recent findings scheduled for publication this year shed new light on this disorder that has baffled scientists for many years.

Advance: These reports provide new information and practical diagnostic tools to make an early differential diagnosis between initial stuttering symptoms and normally dysfluent speech typical of young children. The reports also provide updated information concerning risk factors among children, by tracking those who develop chronic stuttering and those who tend to recover. These studies have revealed a considerable gender difference, noting that boys are more likely to experience persistent stuttering. Progress has also been made towards early identification of children at high risk for persistent stuttering using various metrics, such as pattern of stuttering and speech rate measures.

The possible relation of stuttering and its prognosis to other co-existing conditions such as phonological and language development and disorder are also reported. Data examining familial aggregation indicate a strong genetic component to stuttering, revealing differences in genetic liability between subtypes of stuttering. Based on these findings, this group of investigators has initiated a genetic association study aimed at identifying the genes that predispose individuals to stutter.

Implications: These findings have clinical implications for stuttering in very young children and recognizing its heterogeneity. These results also provide better means for (a) differential diagnosis between early stuttering and normal speech, and (b) different subtypes and risk of developing persistent stuttering. In general, this research will help to focus selective treatment for children who are most likely to have persistent stuttering. Further progress in the genetics of stuttering will have far-reaching clinical implications. [secondary B treatment]

Ambrose N and Yairi E: Normative disfluency data for early childhood stuttering. Journal of Speech-Language and Hearing Research 42: 895-909, 1999.

Ambrose N, Cox N and Yairi E: The genetic basis of persistence and recovery in stuttering. JSLHR 40: 567-580, 1997.

Yairi E and Ambrose N: Early childhood stuttering I: Persistency and recovery rates. JSLHR 42, 1999. In press.

Paden E, Yairi E and Ambrose N: Early childhood stuttering II: Initial status of phonological abilities. JSLHR 42, 1999. In press.

Watkins R, Yairi E and Ambrose N: Early childhood stuttering III: Initial status of expressive language abilities. JSLHR 42, 1999. In press.

Hall K, Amir O and Yairi E: A longitudinal investigation of speaking rate in preschool children who stutter. JSLHR 42, 1999. In press.

Defining a Phenotype for Specific Language Impairment

Background: Specific Language Impairment (SLI) is a disability in the use of language in the absence of any other cognitive disorders. It is estimated that as many as 8% of all school-age children experience SLI. The onset of this disorder occurs during the preschool years, when language fails to develop at an expected rate. While some children appear to outgrow their early language delays, a substantial proportion of individuals with SLI continue to experience problems in a variety of language-related skills including reading, mathematics and oral language through the school years and beyond. Thus, SLI is a disorder of early childhood that can continue to have significant consequences throughout the life span, especially if left undiagnosed and untreated.

Despite research efforts including investigations into the genetic basis and neuoroanatomical characteristics associated with SLI, there has been limited uniformity in the definitions and measures that are used to identify preschool-aged children with SLI. In addition, there has been no consensus about how to identify SLI in older children, adolescents or adults. For complex developmental disorders such as SLI, a clear definition of the disorder is not straightforward, because of the heterogeneity that is characteristic of this disorder. This lack of clear definition and measures of SLI appears to be changing.

Advance: A recent workshop, involving leaders in the field of child language disorders, identified definitional guidelines and research directions that will lead to enhanced abilities to diagnose, assess and ultimately treat the problems associated with this complex language-based disorder. Promising measures to determine a clear diagnosis of SLI have recently emerged. Investigators have found that a brief non-word repetition task, designed to minimize biases associated with traditional language tests, is a powerful predictor of SLI, differentiating children who will benefit from language intervention from children developing language normally.

Implications: This procedure may have considerable clinical utility as a screening measure for SLI in children.

Tager-Flusberg H and Cooper J: Present and future possibilities for defining a phenotype for specific language impairment. Journal of Speech, Language, and Hearing Research, 1999. In Press (manuscript attached).

Dollaghan C and Campbell TF: Nonword repetition and child language impairment, JSLHR 31: 1136-1146, 1998.

Understanding the Causes of Hermansky-Pudlak Syndrome

Background: Hermansky-Pudlak Syndrome (HPS) is a hereditary disorder characterized by reduced pigmentation of the eyes and skin (albinism), a tendency to bleeding, inflammatory bowel disease and progressive fibrosis of the lungs (scar tissue restricts the inflation of the lungs). The disease is usually diagnosed during childhood and often leads to death by age 40 or 50, often as a consequence of fibrosis of the lungs or the inflammatory bowel disease.

Although a gene (*HPS1)* that is responsible for a form of the disease in a subset of patients had been previously identified, subsequent studies demonstrated that not all HPS patients have mutations in this gene. A clue to other defective genes that might produce this syndrome was provided when researchers identified a protein complex, named AP-3, which was involved in protein transport within cells. Fruit flies with mutations in AP-3 exhibited pigmentation defects due to abnormal development of pigment granules. Interestingly, there are also strains of mice, called *pearl,* which suffer from the mouse form of HPS, and have a genetic defect in AP-3. This observation raised the possibility that mutations in AP-3 could be a cause of HPS in humans.

Advance: Researchers screened cell cultures from the skin of HPS patients and identified two siblings whose cells displayed drastically reduced levels of AP-3 protein. This was due to a mutation in a specific subunit of the AP-3 complex. Because of this mutation, some patients suffering from Hermansky-Pudlak syndrome (HPS) bear defects in the machinery that delivers proteins to different compartments of the cell.

Implications: The identification of AP-3 mutations in these patients allowed the development of genetic screening tests for this form of the disease, and established for the first time that defects in the machinery that delivers proteins to the cells can be the cause of human diseases. This principle is now being applied to the study of patients with other forms of HPS and related hereditary disorders.

Dell'Angelica EC, Shotelersuk V, Aguilar RC, Gahl WA and Bonifacino JS: Altered trafficking of lysosomal proteins in Hermansky-Pudlak syndrome due to mutations in the beta3A subunit of the AP-3 adaptor. Molecular Cell 3: 11-21, 1999.

Shotelersuk V, Dell'Angelica EC, Hartnell L, Bonifacino JS and Gahl WA: Oculocutaneous albinism, absent platelet dense bodies, and persistent neutropenia in brothers with mutations in beta3A-adaptin gene: a new variant of Hermansky-Pudlak syndrome. Submitted.

Daylight Sets the Biological Clock through Photoreceptors Unrelated to Vision

Background: Cycles of sleep and wakefulness are under the control of genetic programs that act as biological clocks. On the front line of the biological timekeeping mechanism, the eye mediates the daily resetting of this clock by sunlight and helps maintain 24-hour rhythmicity. Clock-resetting defects may cause sleep and wakefulness to be poorly coupled with periods of day and night. Therefore, understanding the causes of such defects is an important target of sleep research.

Advance: Recent studies with genetically engineered mice whose retinas lack the rods and cones responsible for vision have shown that the light-resetting signal does not originate from these structures in the retina but from a circadian factor unrelated to vision. The newly identified circadian factor named cryptochrome is a leading candidate. In mice lacking the cryptochrome genes, light is less effective in resetting the clock mechanism and there is a loss of daily clock rhythm.

Implications: The genetic program of the circadian clock controls the daily rhythmicity and other properties of the sleep-wake cycle. Disorders of sleep, whether disturbances in the duration or quality of sleep, as with insomnia, or disturbance in the timing of the sleep-wake cycle, as occurs in shift workers, account for considerable dysfunction and morbidity in the general population. The importance of genes to biological timekeeping is underscored by recent genetic-epidemiological findings that individual preferences toward sleep and wake times correlate with the specific type of clock gene inherited. Advances in understanding the human clock program should help reveal the molecular events governing the biological timing of innate rhythms such as sleep and wakefulness and improve our ability to diagnose, prevent, and treat sleep disorders and control sleepiness.

Freedman, MS et al.: Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors. Science 284: 502-504, 1999.

Sleep Apnea in Early Childhood Is Associated With Asthma and Hypertension

Background: Sleep apnea is a disorder characterized by brief interruptions of breathing during sleep. These breathing pauses are almost always accompanied by snoring, although not everyone who snores has this condition. In adults, sleep apnea is widely recognized as a risk factor for hypertension, heart attack, and stroke. Recent studies suggest that children with sleep apnea are also at increased risk of cardiorespiratory diseases.

Advance: An epidemiological study including almost 400 children has provided the first evidence that children with symptoms of airway inflammation are more likely to have sleep apnea than other children. The study showed that the risk of apnea was four times greater in asthmatic children than in normal children, five times greater in children with sinus problems, and seven times greater in children with Awheezing@ problems. A second study has provided the first evidence that sleep apnea can cause high blood pressure in children as young as 2 years of age. It found that elevated diastolic blood pressure was associated with both mild sleep apnea and snoring, but that the rise in diastolic blood pressure was significantly higher in the children with sleep apnea than in children who only snored.

Implications: Extrapolating from findings in adults, undiagnosed sleep apnea can be expected to predispose children to cerebrovascular and cardiovascular disease, excessive daytime sleepiness, and performance deficits. Uncovering a connection between sleep apnea in children and asthma and hypertension is a first step to understanding why this occurs, and may lead researchers to determine how to treat children at risk. With sleep apnea occurring in 1 to 3 percent of preschool children, prevention of the development of asthma and hypertension in apneic children would have significant public health benefit. [secondary B prevention]

Redline, S, et al.: Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. Am J Respir Crit Care Med 159(5 Pt 1);1527-32, May 1999.

Marcus CL, et al.: Blood pressure in children with obstructive sleep apnea. Am J Respir Crit Care Med 157(4 Pt 1):1098-103, April 1998.

Imaging Agent May Provide Information about Recovery after Revascularization

Background: Patients with chronic coronary artery disease and dysfunction of the left ventricle (the major pumping chamber of the heart) are at risk of congestive heart failure and heart attack. Their physicians face important treatment decisions that would be better informed if the ability existed to distinguish between potentially reversible regional heart dysfunction and irreversible regional heart dysfunction.

Advance: Researchers have uncovered a new approach to obtaining useful information, prior to revascularization surgery, about the potential for functional recovery in patients with chronic coronary artery disease and left ventricular dysfunction. A recent study involving 26 patients used an injected imaging agent (a type of ammonia moleculeB^{13}N-ammonia) that had already been found to provide a good measure of blood flow to the heart muscle. The investigators found that ^{13}N-ammonia uptake measured late after injection provides additional insight into the ability of the heart muscle to remain viable that extends beyond its value as a tracer of blood flow. Use of this agent may thus allow physicians to predict more accurately which patients are likely to experience good recovery of heart function after undergoing revascularization.

Implications: Despite the trend of decreasing death rates for ischemic heart disease and stroke, the prevalence of heart failure and resultant death rates in the United States almost tripled between 1974 and 1994. Coronary heart disease is the most common cause of congestive heart failure in developed countries. Among patients with preoperative left ventricular dysfunction in whom revascularization entails high perioperative morbidity and mortality, accurate assessment of myocardial viability may result in more individually tailored treatment plans, more appropriate utilization of resources, and enhanced efficiency of health care delivery.

Kitsiou AN, Bacharach SL, Bartlett ML, Srinivasan G, Summers RM, Quyyumi AA, Dilsizian V: ^{13}N-ammonia myocardial blood flow and uptake: relation to functional outcome of asynergic regions after revascularization. J Am Coll Cardiol 33(3):678-686, 1999.

Why Do Some People Like Addictive Drugs?

Background: One of the most challenging problems in addiction is to understand why after that initial drug experience some individuals continue to abuse drugs whereas others do not. Indications of a neurobiological basis for the pleasurable effects of drugs have been suggested from studies of various animal models. These studies have consistently shown that the neurotransmitter dopamine is an important mediator of the pleasurable effects of virtually all drugs of abuse as well as many natural events that people find pleasant such as eating and drinking. In particular it has been suggested that brain levels of the dopamine D2 receptor, which is involved in the communication among dopamine containing cells, may predict which individuals are more vulnerable to abusing and becoming addicted to drugs. Now with the advances in neuroimaging technology, such as positron emission tomography (PET), in which receptors can be assessed in awake, behaving human beings, scientists have a powerful new tool to begin to unravel the neurobiological substrates that are involved in addiction vulnerability.

Advance: Using PET neuroimaging techniques, scientists have measured both the amount of brain dopamine D2 receptors in the brain as well as measured the subjective responses to the drug methylphenidate in the same individuals. Methylphenidate is a psychostimulant drug that works in the brain in a similar manner to cocaine, but does not have the same powerful euphoric effects that cocaine does. In this study, researchers observed that those individuals with relatively lower levels of brain dopamine D2 receptors found methylphenidate to be Apleasant.@ Individuals with more brain dopamine D2 receptors on the other hand found methylphenidate to be Aunpleasant.@

Implications: The findings reported in this study are the first evidence in humans revealing a direct association between dopamine D2 receptor levels in the brain and the pleasurable effects of psychostimulants. That is, for the first time, the number of receptors has been correlated directly with the Apleasantness@ of a drug. These findings have significant implications for individual differences in how much a person likes a drug and may represent a critical component in the neurobiological basis for drug abuse and addiction vulnerability.

Volkow, ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Gifford A., Hitzemann R, Ding YS, and Pappas, N. Brain dopamine D2 receptor levels predict reinforcing responses to psychostimulants in humans. American Journal of Psychiatry, in press.

Nerve Cell Growth And Development Studies Open Window To New Diagnostic Techniques

Background: The human nervous system carries millions of impulses every hour, messages going both into the brain and out, allowing us to see, speak, and move, as well as making it possible to drive a car, catch a ball, remember what happened six months ago or six minutes agoBand read the words on this page. All of these activities depend on the smooth and coordinated flow of impulses throughout the nervous system, a process that in turn demands intact and normally developed nerve cells, or fiber pathways, in the brain and central nervous system.

The basic operative unit of the nervous system is the *neuron*, the cell that transmits messages from other neurons, using a long thin extension of the neuron called the *axon*. The speed and clarity at which message impulses move within the brain and nervous system depends on several factors, including the diameter of the axon, and while it is clear that the integrity of neurons depends on normal growth and development, scientists have not been certain of the rate of growth, the importance of that rate, or the implications of growth for vital functions such as coordination and speech. Other studies have also raised concerns regarding the role of abnormal or delayed growth in the nervous system as a causative factor in diseases (notably schizophrenia), and suggested that some form of reliable measurement of neuron growth might contribute to diagnostic possibilities. Before now, however, we could not look at living human brains *in vivo* (that is, inside the body) and either verify or calculate rates of growth or maturation.
Advance: Using magnetic resonance imaging (MRI), the research team performed brain scans on 114 children aged of 4-17. Analysis of the images confirmed significant age-related increases in diameter of the fiber pathways, both supporting and clarifying the idea that neuron growth and development is linear, progressive, and continues over the course of childhood and adolescence.

Implications: Aside from a general confirmation that neuron growth is indeed a continual process throughout childhood and adolescence, the researchers noted that the brain centers responsible for both motion and speech were specifically developed, suggesting that the long-term growth of the nervous system=s fiber pathways support the on-going maturation of both movement and speech into the teen years. The nature of this research itselfBusing an MRI scanner with comprehensive analysis of the imagesBestablishes a foundation for measuring rates of growth in the living human brain. Guidelines for normal vs. abnormal rates of growth in the brain can be clarified, and from there the information can be linked to specific disease states, offering an opportunity for significantly improved early detection programs of various neurological and psychiatric abnormalities.

Paus T, Zjidenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, Rapoport JL, Evans A: Structural maturation of neural pathways in children and adolescents: in vivo study. Science 283: 5409 (1999).

Association of Gene Polymorphisms, Tobacco Carcinogens and Lung Cancer

Background: Cigarette smoking is the major risk factor for lung cancer, but susceptibility also depends on the genetic makeup of each individual. To cause harm, most carcinogens in tobacco smoke must first be activated by specific enzymes produced by the body, and inherited variations (or polymorphisms) in these enzymes can alter an individual's risk for cancer.

Advance: By studying 341 patients with lung cancer and 456 healthy individuals, researchers at the University of Hawaii determined that smokers who carried a particular variant of a carcinogen-activating enzyme had a 2.4-fold increased risk of squamous cell carcinoma (SCC), a common type of lung cancer that occurs centrally on the main bronchi or airpipe. The risk of SCC escalated even further (3.1-fold) if the smoker also lacked both copies of a carcinogen-deactivating gene known as GSTM1. Additional analyses revealed that variations in a different enzyme, known as CYP2E1, were associated with a reduced overall risk of lung cancer and, in particular, a reduced risk of adenocarcinoma, a type of tumor that often occurs at the periphery of the lungs. The findings help to clarify the roles of specific tobacco smoke constituents and metabolic pathways in the causation of common types of lung cancer.

Implications: Over the past 50 years, researchers have observed a striking shift in the frequencies of two types of lung tumors, with the once-rare adenocarcinoma displacing SCC as the most prevalent type. The Hawaiian study suggests that polymorphisms in carcinogen-metabolizing enzymes may influence the type of lung cancer that develops in smokers. The findings also support the notion that a reformulation of American cigarettes--and concomitant changes in tobacco smoke carcinogensBmay have contributed to the recent shift in tumor frequencies.

Le Marchand L, Sivaraman L, Pierce L, Seifried A, Lum A, Wilkens LR, and Lau AF: Associations of CYP1A1, GSTM1, and CYP2E1 polymorphisms with lung cancer suggest cell type specificities to tobacco carcinogens. Cancer Res. 58: 4858-63, 1998.

New Technology Provides Molecular Basis of Tuberculosis Pathogenesis and the Potential for Rational Design of New Vaccines and Diagnostics

Background: Tuberculosis is a disease that has plagued mankind since ancient times. It is caused primarily by the bacterium *Mycobacterium tuberculosis* and sometimes by other subspecies such as *M. bovis*. The current vaccine, developed by Calmette and Guérin and called BCG, was generated through growth in culture (passaging) of *Mycobacterium bovis* 230 times between 1908-1921. Because the technology did not exist for preserving strains, it was necessary to continuously grow the organism in a number of places worldwide. As a result, the BCG vaccine is no longer a single strain, but has evolved into a group of related, daughter strains which seem to have variable vaccine efficacy. Moreover, when the BCG vaccine is unsuccessful in preventing contraction of tuberculosis, the vaccine nonetheless obstructs diagnosis of the infection. The coming decade could see 80 million cases of tuberculosis worldwide. Given this projection, the fact that cases of drug-resistant tuberculosis are increasingly common, and the fact that the BCG vaccine has limited effectiveness, particularly in populations other than young children, there is an urgent need for a new vaccine. An approach to designing such a vaccine is to compare the genetic material (DNA) present in *M. tuberculosis* with that in *M. bovis* and the multiple BCG daughter strains.

Advance: Investigators used the new DNA microarray technology to do these comparisons in a much more efficient manner than could be done previously. Microarrays allowed comparison of the genetic material of over a dozen strains by placing the DNA on microchips and determining their ability to bind to one another (hybridize). The results are analyzed with fluorescent dyes. After making such comparisons, investigators identify regions that are present in one strain and absent in others. They also can study historical reports of the BCG vaccines made and used in different countries, and compare the clinical results of those vaccinations and the molecular results of the DNA sequences.

Implications: The information from these studies could lead to rational approaches for the design of improved diagnostics and vaccines. By identifying regions in *M. tuberculosis* that are missing in BCG, scientists may be able to develop a highly specific tuberculosis diagnostic test that can identify tuberculosis infection even when a person has been vaccinated with BCG. This test would be important for those countries with a low prevalence of disease that wish to introduce vaccines, and also for those countries where BCG is used and a more discriminating treatment of latent tuberculosis cases is needed. By comparing different BCG strains, researchers hope to develop a better understanding of the genetic basis for BCG vaccine efficacy. Additionally, because the BCG strains derived from *M. bovis* have much less ability to cause disease than *M. tuberculosis*, comparative molecular studies indicate parts of the genetic material involved in pathogenesis. Thus, these studies have important implications for tuberculosis vaccine design.

Behr MA, Wilson MA, Gill WP, Salamon H, Schoolnik GK, Rane S & Small PM: Comparative genomics of BCG vaccines by whole-genome DNA microarray. Science 284: 1520-1523, 1999.

Hypohidrotic Ectodermal Dysplasia

Background: The hypohidrotic ectodermal dysplasia story dates back to 1875, when Darwin described a peculiar disorder that appeared in each generation of one family's male members. The condition became apparent in the very young, manifesting itself with poorly developed teeth, sparse hair on the head and body, and excessively dry skin due to underdeveloped sweat glands. These characteristics were the origin of the disorder's nameB"hypohidrotic" referring to low levels of perspiration, and "ectodermal dysplasia" meaning abnormal development of certain tissues derived from embryonic ectoderm (teeth, hair, nails, glands).

Advance: In 1996, the gene ED1 was identified for the major X-linked forms of the disease. This year, the gene for the autosomal forms was mapped to chromosome 2. The gene (DL) codes for a protein related to the tumor necrosis factor receptor family. The gene was discovered in the downless mouse mutant, which mimics the human condition. This discovery has led to the identification of a possible interaction between the ED1 protein (a signaling molecule) and the DL protein (a receptor).

Implications: Identification of the genes for ectodermal dysplasia (ED) advances our understanding of the developmental processes involved in formation of skin, hair, and teeth. Earlier diagnosis may be possible for related conditions by searching for mutations in these genes. Future studies may focus on improved treatment for ED, as well as for treatment of other skin conditions, resulting from burns and other trauma.

Monreal AW, Ferguson BM, Headon DJ, Street SL, Overbeek PA and Zonana J: Mutations in the human homologue of mouse *dl* cause autosomal recessive and dominant hyphidrotic ectodermal dysplasia. Nature Genetics 22: 366-69, 1999.

Teaching a Computer to Diagnose Airway Disease

Background: I n the 1970=s, CT (computed tomography) scan technology, based on mathematical algorithms developed at the turn of the century and then state-of-the-art computers, gave physicians an unparalleled view inside the human body. Soon thereafter, physicians began to generate three-dimensional computer models of body organs, using mathematical techniques developed by computer scientists and mathematicians.

In 1989, engineers and physicists at medical equipment manufacturer research labs developed Ahelical@ CT scanners. In 1994, physicians made use of these new generation CT scanners to acquire detailed images of a large body region during a single breathhold. These physicians turned these images into elaborate three-dimensional models of the interior of anatomic structures in a way that simulated conventional endoscopy.

Advance: This year NIH researchers developed and published a method to use these simulated endoscopies to automatically locate tumors in the air passages of the lungs. Their methods are based on the abnormal shape of airway tumors, use mathematical techniques developed by 19th century mathematicians, and build on more recent image processing methods developed by mathematicians and computer graphics specialists.

Implications: The significance of these methods is that they may allow physicians to diagnose tumors of the airway without the need to pass an instrument down a patient=s throat to see the tumor directly. We are also studying whether these methods can be used to find tumors in other organs without the need for conventional endoscopy, such as colon polyps which are precursors to colon cancer.

Summers RM, Selbie WS, Malley JD, Pusanik LM, Dwyer AJ, Courcoutsakis NA, Shaw DJ, Kleiner DE, Sneller MC, Langford CA, Holland SM, Shelhamer JH. Polypoid lesions of airways: early experience with computer-assisted detection by using virtual bronchoscopy and surface curvature. *Radiology* 208:331-337 (1998).

Novel Imaging Technology for Joint Disorders

Background: Optical coherence tomography (OCT) is a new method of imaging capable of detecting small structural changes that occur in tissues during the earliest stages of disease. The resolution of the OCT system is typically on the order of 5-15 microns (one micron is equal to one millionth of a meter), which is nearly tenfold greater than the resolution of any available clinical technology. OCT was originally developed to image the transparent tissue of the eye, and clinical studies are in progress evaluating its potential for a wide range of eye diseases. In addition to its high resolution, several features make OCT attractive for joint imaging: it is optical fiber based, allowing easy integration with an arthroscope, an instrument for the examination of the interior of a joint; it is compact and portable, making it well suited for an outpatient setting; it is Anoncontact,@ allowing imaging to be performed through air or a transparent medium such as saline; it can be performed at high speeds, allowing information at the cellular level to be obtained from throughout the joint; and it can be used in combination with other techniques, providing biochemical and structural information from tissue.

Advance: Using normal and osteoarthritic cartilage specimens, investigators demonstrated the usefulness of this technology to detect structural abnormalities in cartilage. There was a strong correlation between tissue structure observed in OCT images and the corresponding microscopic examination of the tissue. This included identification of irregularities in cartilage surface and identification of new bone growth. These changes occur early in the pathogenesis of osteoarthritis and before loss of cartilage thickness (narrowing of the joint space, as seen by radiography).

Implications: OCT represents a promising new technology for detecting cartilage abnormalities through ultrahigh-resolution joint imaging. Refinement of this technology and its ultimate clinical use may permit early diagnosis of degenerative joint disorders, evaluation of disease severity and progression, and enhanced understanding of pathological processes within joints.

Herrmann JM, Pitris C, Bourma BE, Boppart SA, Jesser CA, Stamper D, Fujimoto JG, and Brezinski ME: High-resolution imaging of normal and osteoarthritic cartilage with optical coherence tomography. J Rheumatol, in press.

Early Identification of Hearing Impairment

Background: NIH-supported research shows that detection of hearing impairment and intervention within the first six months of life leads to development of better language skills. In March of 1998, the NIH convened a Working Group on Early Identification of Hearing Impairment to provide advice on the most pressing research questions regarding diagnostic and intervention strategies following neonatal hearing screening. Based on these research recommendations, a Program Announcement with Set-Aside Funds was published in October 1998 for FY2000 funding for grant applications focusing on intervention strategies following identification of neonatal hearing impairment. Applications were encouraged that address relevant issues including, but not limited to: hardware (hearing aids, cochlear implants and other sensory aids); behavioral treatment programs; development of outcome measures to determine the benefit of intervention strategies; and, studies on the efficacy of intervention. Approximately $1 million in direct costs has been made available for the first year of support. It is anticipated that up to five awards will be made. Applications in response to the first of three receipt dates, (Feb 18, 1999, Jun 18, 1999, Oct 18, 1999) have now been received and reviewed. We anticipate funding one application from the first submission round and expect to receive additional meritorious applications in the near future.

Advance: Data collection was completed in 1998 for a five-year multi-center study on neonatal hearing impairment. The goal of this study is to develop optimal procedures for neonatal hearing screening. This study is the first truly randomized controlled comparison of three different measures of physiological response to hearing in neonates, validated by an independent measure of hearing. This is in sharp contrast to previous studies in which only those infants who Afailed@ the neonatal hearing screening test were followed. All three measures performed equally well in a variety of test environments, including the NICU, well-baby nursery and outpatient clinics, at predicting hearing status at 8-12 months of age.

Implications: The data demonstrate that a significant group of infants whose hearing is normal at birth appear to lose hearing during the first year of life. It will be necessary to monitor auditory function during this period to ensure that hearing loss is detected in a timely fashion.

Yoshinaga-Itano C et al: Language of early- and later-identified children with hearing loss. Pediatrics 102: 1161-1171, 1998.

A New Screening Tool for Lung Cancer

Background: Lung cancer, the leading cause of cancer death for men and women in the United States, claims the lives of an estimated 160,000 people in this country annually. This troubling statistic stems in large measure from our limited ability to detect lung cancer at an earlier and potentially more curable stage. Using available detection methods, most people are diagnosed in advanced stages of disease and only slightly more than 12 percent survive 5 years. Survival improves dramaticallyBto 70 percentBwhen the disease is identified and treated early. Clearly, an effective screening tool for lung cancer would enable early detection and reduce the number of lung cancer deaths, but until recently, none has been available to physicians. Annual chest x-rays, for example, have not been shown to be useful and alternative methods are too costly to be used for routine screening. Now, advances in imaging technology have led to the development of a promising technique, low radiation dose spiral computed tomography (spiral CT). Spiral CT can scan the entire lungs, from the neck to the diaphragm, in less than 20 secondsBa single breath-hold. Rapid scanning minimizes radiation exposure and improves the detection of smaller lesions since they are not moving in and out of the field of view due to breathing. This new tool may prove to be the first screening method to find some types of lung tumors early and reduce lung cancer deaths.

Advance: In the Early Lung Cancer Action Project study, NIH-supported researchers recently tested the effectiveness of spiral CT as a screening tool for lung cancer. The 1000 symptom-free participants of the study, considered to be at high-risk for lung cancer because of their age (60 years or older) and cigarette smoking history (a minimum of 10 pack-years; one pack year is equivalent to one pack of cigarettes smoked per day for one year), were given baseline and annual spiral CT examinations. The researchers demonstrated that, compared to chest x-ray, spiral CT is a considerably more effective tool for detecting small non-calcified lung nodules and thus, for detecting lung cancer at an earlier and potentially more curable stage. Malignant tumors were detected four times as often with spiral CT as with chest x-ray, and stage 1 tumors were detected six times as often with spiral CT as with chest x-ray. This technology, however, may be less useful in clinical application for detecting central airway tumors, such as squamous cell carcinomas, and very rapidly growing carcinomas, such as small cell lung cancers.

Implications: The opportunity to use spiral CT to safely and reliably screen for lung cancer offers new hope to those who are at increased risk for this disease. The cost of this technique is only slightly more than conventional chest x-ray. In addition, elective surgery of small stage 1 lung cancers is less costly than treating later-stage lung cancers. Further research is needed to determine whether lung cancers detected through routine screening actually are more effectively treated and how the size of the tumor at the time of detection may affect the rate of cure. Yet, by enabling physicians to find lung cancer at an earlier and more curable stage, routine screening with spiral CT promises to reduce the number of lives lost to lung cancer.

Henschke CI, McCauley DI, Yankelevitz DF, et al.: Early Lung Cancer Action Project: Overall design and findings from baseline screening. Lancet 354: 99-105, 1999.

Magnetic Resonance Imaging of Cartilage May Aid Early Diagnosis, Treatment of Osteoarthritis

Background: Osteoarthritis, a major cause of disability in the over-50 population, affects more than 40 million Americans and imposes considerable expense on the health care system. There is no known cure for this debilitating disease, and current treatments focus only on symptomatic relief. A major hindrance to the study and treatment of osteoarthritis has been the lack of reliable methods for early detection of disease and for monitoring disease progression and response to treatment.

Advances: To enable early diagnosis of osteoarthritis, scientists at a magnetic resonance imaging (MRI) resource at the University of Pennsylvania are developing noninvasive techniques for detecting subtle degenerative changes in cartilage, which is the primary pathology associated with the disease. The researchers used a new sodium MRI technique to image both healthy bovine cartilage and cartilage that had been partially degraded by the enzyme trypsin, which mimicked the cartilage deterioration seen in osteoarthritis. The new imaging technique revealed several unique properties of the degraded cartilage, including increased permeability and reduced elasticity. The imaging approach lends insight to the design of future in vivo experiments.

Implications: These promising new imaging methods may one day enhance physicians' abilities to diagnose osteoarthritis, intervene with appropriate therapeutics, monitor clinical outcomes, and evaluate potential new therapies, including cartilage-protecting drugs and gene therapies. [secondary B treatment and diagnosis]

Kaufman JH, Regatte RR, Bolinger L, Kneeland JB, Reddy R, and Leigh JS: A novel approach to observing articular cartilage deformation in vitro via magnetic resonance imaging. Journal of Magnetic Resonance 9:653-62, 1999.

Hypothyroidism During Pregnancy Linked to Lower IQ for Child

Background: The thyroid gland is found in the neck and produces hormones important for protein synthesis in virtually every body tissue and is also vital for increasing the cell=s use of oxygen. Hypothyroidism is a condition where the gland does not produce enough hormones, resulting in fatigue; coarse, brittle hair; thick, coarse skin; and a lowering of the body=s metabolic rate. But, in many cases, the disorder goes undetected because there are no obvious physical signs or symptoms. When hypothyroidism occurs simultaneously in a pregnant woman and her fetus, the child=s neuropsychological development may be adversely affected.

Advance: In a recent retrospective study, researchers determined that children born to mothers with untreated hypothyroidism during pregnancy scored significantly lower on IQ tests than children of healthy mothers. The children ranged from 7 to 9 years at the time of the study and participated in a series of psychological tests relating to intelligence, attention, language, reading and school problems, and visual-motor performance. In these children, 15% had IQ scores lower than 85, compared to only 5% of the control children. Overall, the affected children scored poorer on all 15 individual tests than the children born to healthy mothers. Of the 62 women in the study who had hypothyroidism, 48 did not receive treatment during pregnancy for their condition. Of their children=s IQ scores, 19% were below 85. However, the children born to mothers who had received treatment scored similarly to the control children, suggesting that treatment can help lessen the adverse effects.

Implications: This study suggests that hypothyroidism might be added to the group of correctable maternal conditions that can influence the long-term health of the child. Hypothyroidism can be determined by measuring thyroid stimulating hormone (TSH) levels in the blood. High TSH levels serve as an early warning that the thyroid is not functioning adequately. The condition can then be treated with medication (thyroid hormone). These findings suggest that early detection and treatment for hypothyroidism of the mother during pregnancy might be an important factor in the intelligence and well-being of her child. Additional research is needed to form the basis for maternal screening policies.

Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O=Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, and Klein, RZ: Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. New Engl J Med 341: 549-555, 1999.

Determining Accurate Placement of Feeding Tubes

Background: Each year in the U.S. there are about one million patients or nursing home residents who are tube-fed. A common event in any care setting, including in the home, is displacement of the feeding tube from its proper location. Either upon insertion of the feeding tube or at any time after insertion, there is potential for the tube=s location to be displaced such that tube feeding contents may be directed into the respiratory tract. That event is potentially fatal and, at best, results in morbidity and additional health care costs.

Current clinical methods that do not utilize x-rays to determine the placement of feeding tubes are accurate from 6 to 34% of the time. X-rays of the abdomen are the most accurate determination of correct placement, and are often required by policy upon insertion or reinsertion of a feeding tube before tube feedings can begin. However, movement by the patient or transfer of the patient from bed to chair, or unknowing removal of a feeding tube by the patient himself, may require x-rays with each subsequent event of full or partial dislodgement in order to ascertain correct placement of the reinserted or repositioned feeding tube. The current study evaluated a new, noninvasive method of verifying correct feeding tube placement by using limited chemical analysis. The analysis was performed on aspirated material once a feeding tube has been inserted/replaced.

Advance: The study validated a method of estimating placement of feeding tubes by determining pH and bilirubin levels in the aspirated contents from a feeding tube. The combination of pH levels and bilirubin levels resulted in the correct identification of all instances of improper placement of the feeding tube into the respiratory tract. Similarly, correct placement in either stomach or intestines was identified correctly in most instances.

Implications: The study developed and validated a method to determine proper placement of feeding tubes that is quicker and less costly than the current use of x-rays. The study method identified all instances of placement of the feeding tube in the respiratory tract, an event which has consequences of high morbidity and mortality. The study method saves costs of x-rays, as well as attendant discomfort to the patient.

Metheny NA, Stewart BJ, Smith L, Yan H, Diebold M, Clouse RE. pH and concentration of bilirubin in feeding tube aspirates as predictors of tube placement. Nursing Research 48:189-197, 1999.

Guidance for Treating Patients with Brain Aneurysms

Background: A brain or cerebral aneurysm is a weak spot in the wall of a cerebral artery that balloons out due to pressure from the blood. When a brain aneurysm ruptures, it releases blood into the area surrounding the brain (a subarachnoid hemorrhage) causing a hemorrhagic (bleeding) stroke. Hemorrhagic strokes account for about 20 percent of all strokes, but they are more lethal than strokes due to an obstruction of blood flow to the brain, causing about 80 percent of all stroke-related deaths. Surgery can repair aneurysms, but brain surgery carries its own risks, including stroke or infection that can impair mental ability, damage the brain, or even cause death. Perhaps as many as 10-15 million Americans may have intracranial aneurysms at some point in their lifetimes, but most aneurysms do not rupture. The lack of information about the natural history (development risks, size, location, risk of rupture) of unruptured intracranial aneurysms and about the risks of surgery has hampered physicians and patients in deciding whether surgical treatment is warranted in a particular case.

Advance: A new study followed 2621 patients at 53 centers in the United States, Canada, and Europe. The study examined in detail how the size and location of the unruptured aneurysm and the patient=s medical history influence the likelihood that an aneurysm will burst. The researchers also monitored the frequency and severity of problems following surgery for an unruptured aneurysm to gauge the risks associated with surgical intervention. The study found, for example, that the likelihood an unruptured intracranial aneurysm less than 10mm in diameter would burst was exceedingly low in patients without a history of subarachnoid hemorrhage. With this information in hand, patients and their physicians can make a better informed choice about treatment.

Implications: The results provide much needed guidance for the treatment of unruptured brain aneurysms. Each patient=s situation is different, and patients must discuss their prospects with their physicians, but with this new information many patients with small aneurysms and without a history of brain hemorrhages may choose to avoid surgery and be comforted by the prospect of living a normal lifestyle with minimal risk while monitoring the aneurysm.

The International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysmsCrisk of rupture and risks of surgical intervention. NEJM 339:1725-33, 1999.

Understanding the Causes of Preeclampsia

Background: The placenta is a specialized organ that is critical to the maintenance of pregnancy. Abnormalities in placenta function can lead to life-threatening conditions for both mother and fetus. One such condition, preeclampsia, is a disorder that adversely affects approximately 7-10% of first-time pregnancies and is the leading cause of maternal death in the U.S. Besides causing dangerously high blood pressure, kidney failure, and seizures in the mother, children born to mothers with preeclampsia may be born prematurely or may have a low birth weight. The cause of the condition is unknown. One hypothesis is that it results from poor blood vessel development between the placenta and the uterus. Another hypothesis is that an imbalance between chemicals that raise (thromboxane) and lower (prostacyclin) blood pressure in pregnancy causes preeclampsia.

Advance: In two separate studies, researchers have made substantial contributions to understanding normal and abnormal functions related to preeclampsia. In one study, researchers have uncovered basic mechanisms involved in the normal formation of blood vessels between the placenta and uterus and have shown that certain aspects of these mechanisms are different in preeclampsia. In addition, these investigators have shown that specialized placental cells (cytotrophoblasts) in direct contact with uterine cells undergo a high rate of apoptosis, or Acellular suicide,@ in preeclamptic placentas compared to normal ones. Consequently, the placental connection between the mother and the fetus is compromised.

In another study, researchers collected urine samples from a large population of women early in pregnancy. Those who developed preeclampsia and a comparison group of normal pregnant women had these samples tested for the chemicals prostacyclin and thromboxane after they gave birth. The study revealed that prostacyclin levels are significantly lower in women destined to develop preeclampsia months before symptoms appear, and that the ratio of thromboxane to prostacyclin is elevated in women who develop preeclampsia, from the second trimester onward. Thus, subnormal prostacyclin and thromboxane-prostacyclin ratio abnormalities play a key role in developing clinical preeclampsia, either as a cause or an early abnormality.

Implications: These important discoveries provide significant new information on the cause of preeclampsiaBsuggesting possible avenues for early diagnosis and prevention of a potentially fatal condition. In addition, results from one study have already laid the foundation to develop possible treatments for this condition. For example, previous trials have tried, often unsuccessfully, to prevent preeclampsia by giving aspirin to block thromboxane. Now, researchers have developed an important new strategy for preventing preeclampsia that focuses on increasing levels of prostacyclin, rather than blocking thromboxane.

Mills JL, DerSimonian R, Raymond E, Morrow JD, Roberts LJ, Clemens JD, Hauth JC, Catalano P, Sibai B, Curet LB, and Levine RJ: Prostacyclin and thromboxane changes predating clinical onset of preeclampsia: A multicenter prospective study. JAMA 282: 356-62, 1999.

DiFederico E, Genbacev O, and Fisher SJ: Preeclampsia is associated with widespread apoptosis of placental cytotrophoblasts within the uterine wall. Am J Pathol 155: 293-301, 1999.

Biomolecular Underpinnings of Acute Human Leukemias

Background: Acute human leukemias are associated with chromosomal alterations of genes that encode two related proteins, the alpha and beta forms of core binding factor (CBF). CBFalpha binds to a specific region of DNA and helps regulate genes that aid blood and bone development, whereas CBFbeta complexes with CBFalpha to increase affinity for the DNA binding sites. The structural details of the interactions between the two CBF proteins and DNA are poorly understood.

Advances: Using advanced nuclear magnetic resonance instruments, scientists at Rockefeller University analyzed the three-dimensional structures of CBFalpha and CBFbeta proteins and identified the specific portion of CBFalpha that interacts with DNA. The researchers also found evidence that CBFbeta does not directly associate with DNA but rather stabilizes the DNA-binding surface of CBFalpha, facilitating its interactions with DNA.

Implications: These studies reveal how structural abnormalities in the CBF proteins might prevent or inhibit binding to DNA, and thereby interfere with regulation of blood and bone development. Because abnormalities in CBF proteins have been implicated as contributors to acute human leukemias and other developmental disorders, studying the structure and functions of these molecules can lead to new insights into leukemogenesis and related chromosomal/genetic anomalies. Many of these genetic alterations have important prognostic implications that can guide the selection of therapy. The insights gained from studies of translocation-generated oncogenes and their protein products should hasten the development of highly specific, and hence less toxic, forms of leukemia therapy.

Nagata T, Gupta V, Sorce D, Kim W-Y, Sali A, Chait BT, Shigesada K, Ito Y, and Werner MH: Immunoglobulin motif DNA recognition and heterodimerization of the PEBP2/CBF Runt domain. Nature Structural Biology 6:615-9, 1999.

SCIENCE CAPSULES

GJB2: A Major Cause of Hereditary Hearing Impairment in the United States. GJB2, the gene encoding the gap junction protein connexin 26, has recently been shown to be the gene where mutations cause as much as 30-40% of early-onset hereditary hearing impairment. This discovery has paved the way for development of simple diagnostic test that will be useful in diagnosing hereditary hearing impairment in a substantial number of children. Of particular interest, there is remarkable variation in the time-of-onset and severity of hearing impairment experienced by individuals who carry the same mutation in GJB2, underscoring the importance of modifying genetic and environmental factors.

Cohn ES et al: Clinical studies of families with hearing loss attributable to mutations in the connexin 26 gene (GJB2/DFNB1). Pediatrics 103(3) 546-550, 1999.

Epilepsy Caused by Pig Tapeworms. Neurocysticercosis is an infection of the brain caused by a tapeworm present in undercooked pork and easily transmitted where sanitation is poor. It is a major cause of epilepsy in most developing countries and is an emerging disease within the United States. The mechanism that causes inflammation in the brain is still not clearly understood. International teams of researchers from the U.S. and Peru are searching for mechanisms and innovative therapies, and have developed methods to monitor and determine the effectiveness of current treatments.

Evans CAW, Garcia HH, Hartnell A, Gilman RH, Jose P, Martinez M, Remick DG, Williams TJ and Friedland JS Elevated concentrations of Eotaxin and Interleukin-5 in human neurocysticercosis. Infection and Immunity 66: 4522-4525, 1998.

Improved Genetic Testing for Colorectal Cancer Risk. Genetic testing offers the exciting possibility of identifying predisposed or susceptible individuals so that intervention therapies and careful screening can be started before actual clinical signs of disease. In the case of colorectal cancer, it is already known that people with benign adenomatous polyps might be at increased risk. This is particularly true if these polyps arise from a condition known as familial adenomatous polyposis (FAP). The current genetic test for the *APC* gene, which is implicated in this condition, only reveals 80% of the FAP individuals at risk for developing this cancer. Now, the possibility exists to detect the remaining 20% at-risk individuals. Using a monoallelic mutation analysis (MAMA), NIH-supported researchers were able to assess abnormalities in both alleles independently and to detect inactivating mutations in a way that would complement existing genetic testing for this condition.

Laken, SJ, Papadopoulos, N. Petersen, GM, Gruber, SB, Hamilton, SR. Giardiello, FM, Brensisnger, JD, Vogelstein, B, and Kinzler, KW (1999) Analysis of masked mutations in familial adenomatous polyposis. Proc. Natl. Acad. Sci. USA 96: 2322-2326.

Biomarkers for Oxidative Stress Discovered. Researchers have discovered a new class of molecules that have been implicated in the process of cellular injury caused by oxidation in a wide

variety of human diseases including Huntington=s Disease, Alzheimer=s Disease, atherosclerosis, and kidney disease. Measurement of this important biomarker for oxidative stress could provide a means to evaluate the progression of these diseases and to quantify the body=s response to experimental therapeutic interventions.

Chen Y, Morrow JD, and Roberts LJ, II: Formation of reactive cyclopentenone compounds in vivo as products of the isoprostane pathway. Journal of Biological Chemistry 274: 10863-10868, 1999.

Montine TJ, Beal MF, Cudkowicz ME, O'Donnell H, Margolin RA, McFarland L, Bachrach AF, Zackert WE, Roberts LJ, and Morrow JD: Increased CSF F2-isoprostane concentration in probable AD. Neurology 52: 562-565, 1999.

Montine TJ, Beal MF, Robertson D, Cudkowicz ME, Biaggioni I, O'Donnell H, Zackert WE, Roberts LJ, and Morrow JD: Cerebrospinal fluid F2-isoprostanes are elevated in Huntington's disease. Neurology 52: 1104-1105, 1999.

Psychiatric Disorders and Disability in Refugee Survivors of Mass Violence. A new consideration to be taken into account in developing aid programs for war refugees was highlighted in a recent NIH-funded study that found high levels of disability and functional impairment in a population of refugees from the conflict in Bosnia and Herzegovina who had experienced multiple traumatic events, including torture suffered by one in five. In response to culturally validated measures used by the researchers, 39% of the refugees reported symptoms that meet diagnostic criteria for depression, and 26% reported symptoms meeting criteria for post-traumatic stress disorder (PTSD); 21% reported symptoms comorbid for both disorders. More than one-in-four self-reported having a disability, with the highest rate of disability occurring in those who experienced both depression and PTSD. These high levels of disability and functional impairment among trauma-exposed populations raise concern about the effectiveness of efforts to provide aid if acute and chronic mental health concerns are not addressed.

Mollica RF, McInnes K, Sarajlic N, Lavelle J, Sarajlic I, Massagli MP: Disability associated with psychiatric comorbidity and health status in Bosnian refugees living in Croatia. JAMA 282 (5), 433-439, 1999.

Schaller B: One-quarter of Bosnian refugees may be disabled by psychiatric disorders. Harvard Medical School News August 3, 1999.

Philipkoski K: War trauma could sabotage aid. WIRED News
http://www.wired.com/news/news/culture/story/21157.html August 4, 1999

Risk for Depression in Young Women during Transition to Adulthood. A new study of adolescent girls followed across the transition from high school to early adulthood has ascertained that some 37% of the young women experienced, for the first time, a major depressive episode that had negative impact on their school performance and their intimate romantic relationships. NIH-funded investigators found that, overall, 47% of the young women had experienced one or more episodes of major depression; this higher number includes those who had the illness prior to high school. Risk of recurrence of depression was substantial for all the women**,** and particularly so for those with onsets prior to the study. Women who had psychiatric disorders other than depression also were more likely to have depressive episodes during the post-high school period.

Rao U, Hammen C, Daley SE: Continuity of depression during the transition to adulthood: A 5-year longitudinal study of young women. Journal of the American Academy of Child and Adolescent Psychiatry 38: 908-915, 1999.

The Cumulative Toll of Trauma on Mental Health. Does exposure to one or more traumatic events have any influence on the likelihood that the same person will develop symptoms of post-traumatic stress disorder (PTSD) if he or she experiences yet another traumatic event later in life? Addressing this question in a large community-sample, NIH investigators found that individuals were particularly likely to develop PTSD if a prior traumatic event involved interpersonal violence, especially in childhood. Experiencing multiple traumatic events and being female were also related to the proportion of individuals who developed PTSD.

Breslau N, Chilcoat HD, Kessler RC, Davis GC:. Previous exposure to trauma and PTSD effects of subsequent trauma: Results from the Detroit Area Survey of Trauma. American Journal of Psychiatry, 156: 902-907, 1999.

Flow Cytometry Enables Rapid Genome "Fingerprinting." Scientists at the National Flow Cytometry Resource at Los Alamos National Laboratory have demonstrated a sensitive new technique for rapidly analyzing and characterizing bacterial DNA fragments. The new method uses ultra-sensitive flow cytometry to accurately size and analyze DNA segments in a matter of minutes, compared to the hours required for more commonly used analytical techniques. Further development of this technology may enable bacterial identification and subsequent treatment in hours versus days that are currently required.

Huang Z, Jett JH, and Keller RA: Bacteria Genome Fingerprinting by Flow Cytometry. Cytometry 35:169-175, 1999.

STORIES OF DISCOVERY

Osteogenesis ImperfectaBBrittle Bone Disease

Imagine breaking your ribs when you sneeze. Or fracturing the bones in your spine when the bus you=re riding hits a bump in the road. ABrittle bone disease@ is a genetic defect of collagen, the connective tissue scaffolding upon which bones are built. Technically known as osteogenesis imperfecta, or OI, this mysterious hereditary disorder ranges from mild to severe, depending on the nature of the genetic mutation involved. Mild cases may go undiscovered, but those with the most severe form break so many bones during birth that they do not survive. Some suffer only occasional fractures, breaking about 10 bones in a lifetime; others, with more severe cases may break several hundred.

From 20,000 to 50,000 people may have the disorder, according to the Osteogenesis Imperfecta Foundation. Currently, there is no cure for OI and treatment is usually directed toward preventing bone fractures and caring for fractures that have occurred. Often, people with OI must remain confined to a wheelchair or wear protective braces. Others may undergo a surgical procedure known as Arodding@Bhaving metal rods inserted through the length of the bones to strengthen them and prevent them from breaking.

Diagnosis, too, sometimes proves difficult. OI testing is usually performed by analyzing a skin sample for defective collagen. Although this test can identify most people with OI, about 15 percent of those with obvious signs of the disorder do not have a collagen abnormality that can be detected with the test.

Dr. Joan Marini and her colleagues at NIH have studied the disorder since the 1980s and have unlocked many of its secrets. The NIH researchers began their efforts by pinpointing the numerous mutations that can occur in the gene for Type I collagen, learning that mutations in some parts of the gene cause more severe forms of the disease than do mutations in other parts. This work has resulted in the development of the current methods for diagnosing the condition. Similarly, this research effort provides valuable information on the basic biology of bones, which may be useful in the study of other bone disorders.

For the most part, OI results from only one copy of the abnormal Type I collagen gene. In the past, researchers working with other genetic disorders have tried, with little success, to correct mutations by inserting normal copies of a gene into cells, but this strategy is not suitable for OI.

In contrast, the NIH researchers sought to *prevent* the abnormal collagen from being made. If the defective collagen could be eliminated, they reasoned, OI patients having one normally functioning copy of the gene would experience only a mild form of the disease.

The NIH research team looked to a comparatively new gene technology, which also holds promise for treatment of cancer and AIDS. A plant virusBtobacco mosaic virusBproduces a form of the genetic material RNA that can bind to other types of RNA and prevent them from functioning. Briefly, RNA, or ribonucleic acid, is an intermediary molecule. DNA (deoxyribonucleic acid), the

basic material of genes, gives rise to RNA. In turn, RNA serves as a kind of template upon which proteins are put together.

The tobacco mosaic virus RNA binds to other types of RNA and cuts them into pieces--preventing the proteins they code for from ever being made. Moreover, this particular type of RNA, which scientists have dubbed the Ahammerhead ribozyme,@ can be tailor made to bind to particular kinds of RNA. Taking advantage of that fact, Dr. Marini and her group have engineered ribozymes that break apart the RNA that codes for the defective Type I collagen RNA. The group inserted the ribozymes into laboratory cultures of skin cells from patients with OI and succeeded in stopping the skin cells from producing the abnormal collagen.

Building on this achievement, the group is now exploring ways to introduce the ribozymes into the bone marrow Astem cells@ which manufacture bone. In theory, the stem cells could be removed from a patient and the DNA that codes for the ribozyme could be added to the cells. After reproducing in laboratory cultures, the cells could then be injected back into OI patients.

The NIH researchers also have used genetic engineering to produce a strain of mice having a defective Type I collagen gene. The researchers are now attempting to insert the ribozyme into the cells of these mice in hopes of providing a treatment for their disorder.

Hereditary Hearing Impairment: Gene Discovery and Issues for Clinical Application

About one child in 2000 is born with hereditary hearing impairment that compromises the development of normal spoken language skills. Seventy percent of these children have nonsyndromic hereditary hearing impairment, which is hearing impairment in the absence of other clinical findings. It is estimated that 80% of all nonsyndromic hereditary hearing impairment is inherited in a recessive fashion, where two copies of the mutant gene are needed to cause the disorder. In 1994, the first gene where mutations result in recessive nonsyndromic hereditary hearing impairment (DFNB1) was mapped to a region of human chromosome 13. Three years later, scientists showed that mutations in the GJB2 gene, which encodes the gap junction protein connexin 26, were the cause of deafness in DFNB1 families. Since the discovery of the GJB2 gene, much has been learned by scientists studying the nature of mutations in this gene that cause deafness.

In some population groups (people of Mediterranean origin), mutations in GJB2 account for over 50% of the cases of nonsyndromic recessive hereditary deafness. Within the United States, about 1/3 of all recessive hereditary hearing impairment is caused by mutations in GJB2, and in most cases the same mutation (35delG) is found in different families. However, within one particular ethnic group that shares a common ancestry, the Ashkenazi Jews, almost all cases of recessive hereditary deafness are caused by GJB2 mutations. But in the Ashkenazi Jewish population, the most common mutation in GJB2 (called 167delT) differs from the mutation found in many other Americans (called 35delG). About 3% of all Americans carry one mutant copy of the GJB2 gene, a remarkably high carrier frequency that raises interesting questions regarding the origin and explanation for such a high carrier frequency.

The GJB2 gene is very small, making it straightforward to design a test to screen children with hearing impairment for mutations. Within the last year, several studies have been conducted to correlate the severity and progressive nature of hearing impairment with mutations in GJB2. The results of these studies have important implications for clinicians who might wish to use genetic information about GJB2 for diagnostic or prognostic purposes. First, there was significant variation in the degree, and time-of-onset, of hearing impairment among individuals with exactly the same genetic change in both GJB2 genes (35delG mutation). Given this variation in clinical course, it would be difficult to make any strong predictions regarding an infant found to have GJB2 mutations. Clearly, there are additional modifying genetic and environmental factors that determine the time-of-onset and severity of hearing impairment. Additional research will be needed to define these modifying factors. Second, additional mutations besides 35delG and 167delT were found in some families, making it imperative that any test for GJB2 mutations consider the entire coding region of the GJB2 gene. Finally, there were a few individuals heterozygous for mutations in GJB2 that nevertheless had profound hearing impairment. There are several possible explanations for these findings: (1) GJB2 heterozygosity did not contribute to causing deafness. These individuals were among the 3% of Americans that carry a mutant GJB2 gene, and another gene is responsible for hereditary deafness; (2) GJB2 heterozygosity together with mutations in another as-yet-undefined gene, or genes, resulted in deafness; or (3) the individuals did in fact have two mutant GJB2 genes. One of the mutations, however, was in a region of the gene that was not examined, but was critical

for gene functionBperhaps a region that was essential for the gene to be expressed in an appropriate fashion.

This experience underscores the issues surrounding the use of genetic testing in the clinical setting, at least until the basis for some of these complexities are understood. Coupled with the fact that GJB2 is but one of over twenty genes that can cause recessive hereditary hearing impairment, it is clear that discovering a gene where mutations cause hearing impairment is the critical first step in a longer journey to understand completely the relationship between gene mutation, auditory function, and the progression of hearing impairment.

Turning Blue Babies Pink

In 1944, Eileen Saxon, a blue, frail 15-month-old child weighing little more than a newborn, was anesthetized with drops of ether and woke up a pink pioneer in congenital heart disease. She had the first Ablue baby@ operation conceived and perfected by the team of Alfred Blalock, Helen Taussig, and Vivien Thomas at Johns Hopkins, which revolutionized congenital heart disease treatment. Her postoperative course was rocky. The sophisticated monitoring commonplace in pediatric hospitals today was nowhere in evidence. Instead, the surgical team visited frequently, and a pediatrician set up a stretcher next to Eileen=s bed, remaining by the child=s side continuously for the first 48 hours.

Eileen=s malformation, tetralogy of Fallot, is the most common cause of cyanotic (blue) congenital heart disease. Pathologists began describing the constellation of features from autopsy specimens in the late 1600s, and Fallot, writing in 1888, summarized the four consistent features: a large hole between the 2 pumping chambers of the heart, an underdeveloped blood supply to the lungs, an abnormally positioned aorta, and thickening of the right ventricle. For over 250 years, physicians could only stand by and watch while children with cyanotic heart conditions suffered through childhood, rarely surviving into adolescence. The Blalock-Taussig shunt became the medical equivalent of a shot heard =round the world.

Amazingly, Eileen was taken to the operating room for heart surgery without any direct imaging of her heart to pinpoint the diagnosis. In 1944, doctors had at their disposal only primitive electrocardiography, chest X-rays, and fluoroscopy to augment patient history and physical examination in making a cardiac diagnosis. From these tools, inferences could be made about the shape of the heart and the size of the ventricles, but direct confirmation came only at autopsy. The success of the blue baby operation in providing the first therapy for congenital heart disease led to an explosion of interest in better diagnostic tools. Fortuitously, this coincided with the establishment of the National Heart Institute within the NIH (now the National Heart, Lung, and Blood InstituteBNHLBI) in 1948. From its beginning, the Institute supported research in the new field of pediatric cardiology. In 1950, it awarded Dr. Blalock $12,000 to study surgical approaches to congenital heart disease. His work built on a previous award to Johns Hopkins to study radiographic and angiocardiographic diagnosis of congenital heart disease. Researchers at Hopkins assembled a primitive angiographic apparatus that would advance film cassettes using a rope pulley for serial imaging during the dye injection. More often than not, one of them would have to remain under the contraption, guiding the cassettes so they did not fall on the floor, and simultaneously trying to avoid X-ray beams. From this humble beginning arose modern angiocardiography, which meant that, for the first time, anatomy inside the heart could be visualized in the living child outside the operating room.

Whereas the Baltimore team sought to create a shunt to the pulmonary artery, Dr. Robert Gross was the first surgeon to eliminate a naturally occurring shunt, the ductus arteriosus. This vessel allows blood to bypass the lungs in the fetus, and is programmed to close shortly after birth. Occasionally, however, it does not close, and can overload the left side of the heart, leading to heart failure. In 1938, Dr. Gross was a surgical resident at the Children=s Hospital in Boston. He approached the Chief of Surgery with a proposal to tie off the ductus in a child in whom the diagnosis had been made by auscultation (listening with a stethoscope). The Chief rejected Gross= proposal in no

uncertain terms, but persistence paid off. While the Chief was on vacation, Gross successfully ligated the ductus in a 7-year-old child who survived and did well.

The next major breakthrough was the development of heart-lung bypass, which allowed surgery to be performed on the inside of the heart in a bloodless field. Dr. John Gibbon, a surgeon at the Massachusetts General Hospital, began work on a heart-lung bypass machine in the 1930s. His work was interrupted by World War II, but he resumed it after the war with support from the NIH and collaboration with IBM engineers. His first patient was a 15-month-old baby who died, in part, because her preoperative diagnosis was incorrect. Success came with his second patient, an 18-year-old girl with a hole between the two top chambers of her heart (atrial septal defect), who survived the first heart-lung bypass procedure in 1953. Although many refinements were needed to bring bypass into widespread use, it was a big improvement over previous practices of packing the patient in ice and doing Abeat-the-clock@ surgery, or of so-called cross-circulation, in which the blood supply of a parent and the child were connected, and the parent=s heart provided the circulating pump for the child. This latter procedure has been described as the only surgical procedure with the potential for 200 percent mortality, and it was quickly replaced.

Through courage and resourcefulness on the part of patients and physicians, it had now been demonstrated that both open- and closed-heart surgery were feasible on infants and children. Angiography provided general diagnosis of congenital heart disease, but it was invasive, requiring catheters to be placed through peripheral blood vessels into the heart. With successful surgery becoming more widespread, there was increased interest in developing noninvasive imaging. In 1957, the NIH awarded a grant to Alexander Nadas at Boston Children=s Hospital to study phonocardiography in congenital heart disease. A microphone was placed on the child=s chest so that the sounds made by murmurs and by heart valves opening and closing could be recorded on paper for further study. From these tracings, physicians quantitated the degree of narrowing of heart valves and recognized additional heart sounds that indicated heart disease.

The use of ultrasound waves to visualize the heart (echocardiography) was an astute clinical application of sonar technology developed during World War II. Fuzzy images barely recognizable as the heart were produced for the first time in 1954. The scientific details of echocardiography were worked out largely by physicists and engineers, including Dr. Olaf Von Ramm, a biomedical engineer at Duke University. Dr Harvey Feigenbaum, a cardiologist at the Indiana University School of Medicine was the first to realize the practical potential and to bring echocardiography into clinical practice. Both researchers, as well as many other adult and pediatric cardiologists working on echocardiography, were supported by the NIH and continue to receive NIH funding. Echocardiography was first used in children in the early 1970s. By the 1980s, ultrasound techniques had been refined, color imaging had been added, and image resolution had improved to the point that noninvasive diagnosis of congenital heart defects could be reliably performed in utero. Dr. von Ramm now is applying his energies and NIH funds to develop 3-D echocardiographic imaging, first introduced in 1995. Commercial 3-D systems, now in experimental use in both adults and children, allow researchers to peer inside of hearts in ways that are not possible with conventional 2-D imaging.

Once hearts could be imaged, and congenital heart disease could be diagnosed accurately, epidemiologic studies could be done to determine the patterns of congenital heart defects in populations. The landmark Baltimore-Washington Infant Study, funded by the NIH in the 1980s, is the gold standard for categorizing types of congenital heart disease, estimating their occurrence among live-born infants, and analyzing possible risk factors. From this study we learned that about 1 percent of newborns (about 40,000 per year in the United States) have some form of congenital heart disease, making this the most common birth defect.

A child born 50 years ago with a heart defect had a dismal prognosis. Today, that same child will likely live a long and productive life. Looking back over the past half century, one cannot help but be awestruck by the incomparable progress in pediatric cardiology. In no other pediatric specialty has the medical landscape changed so dramatically, from near-certain mortality at an early age, to prenatal diagnosis and, in some cases, prenatal therapy. Delicate repair of complex congenital heart defects can now be undertaken in the newborn period, on infants weighing as little as 3 pounds. These accomplishments are founded on the courage of families willing to submit their desperately ill children to unproven procedures to forestall death, and to the intellect, persistence, and skill of physicians and researchers who pioneered innovative therapies. The NIH has been a constant partner in the research that supported every step of this miraculous journey, from the development of echocardiography, angiocardiography, and surgical procedures in children to the now common clinical use of genetic testing for abnormalities associated with congenital heart disease. Looking forward to the next 50 years, the NIH has taken the leadership role in supporting research into the molecular underpinnings of normal and abnormal heart development. With new molecular and physiologic tools, understanding the reasons why heart development goes awry may lead to therapies unimagined today.

A New Form Of Type 2 Gaucher Disease

When the body=s red blood cells (RBCs) complete their 4-month lifespan they are sent back to the bone marrow for replacement by fresh RBCs. The old cells are then broken down by chemicals known as enzymes, and the cells= raw materials are recycled by the body. Among these raw materials are fatty substances known as lipids, which must be separated, or Acleaved,@ by specialized enzymesBif not, the lipids accumulate in the body, interfering with critical functions including the circulation of blood and the operations of the nervous system and the brain.

Gaucher (pronounced go-SHAY) disease is created by the inability to breakdown a specific lipid called glucocerebroside, due to an inherited defect in the enzyme glucocerebrosidase. When this enzyme fails to do its job, fatty glucocerebroside builds up, causing congestion and blockage at various sites in the body and creating a form of illness scientists now refer to as a Alipid storage disorder.@ Gaucher disease is the most common of the lipid storage disorders, and has also been termed an Ainborn error of metabolism.@ As that term suggests, Gaucher disease is inherited and interferes with the basic functions of the body, in some cases to the point of death. While the severity of Gaucher disease varies widely in the groups of people it affects, its impact is significant in terms of life and health.

Gaucher disease is named for Philippe Gaucher, the French doctor who first observed the characteristic pattern of symptoms in 1882. Over the next 50 years Gaucher disease was recognized as a genetic defect that, in its most common form, affected people of Jewish ancestry from Eastern Europe, the Ashkenazic Jews. But it was also seen in two other forms, and scientists categorized Gaucher disease variations as Type 1 (the most common form, first described by Philippe Gaucher and now treatable with enzyme therapy), Type 2 (a fatal illness affecting babies, with no ethnic or genetic focus), and Type 3 (a chronic nervous system deterioration, also without specific genetic focus).

In the attempt to learn more about problems like Gaucher disease, researchers have turned to Aanimal models.@ In the past scientists studied naturally occurring diseases in animals that were similar to human forms of the same disease. Now, however, it is possible to genetically alter an animal to create a disease that is ordinarily found in humans and carefully follow every step of that disease=s effects, progression, and outcome.

An animal model can expand our knowledge of what we might expect to see in people affected with a specific disease and, most importantly, how we can help those people. One such animal model that researchers are finding of exceptional value is the Amouse model,@ when mice are genetically altered to create very specific models of human disease. In 1992, NIH intramural researchers created the first Gaucher disease mouse model (the AGaucher mouse@), causing mice to be born without glucocerebrosidase enzyme activity and thereby mimicking the precise problem at the heart of Gaucher disease in humans. The research goal was to learn more about Type 2 Gaucher disease, the most severe form of the illness (invariably fatal for babies, often before their first birthday) and an area where an extension of our knowledge would significantly improve prenatal counseling for families at high genetic risk, as well as offer clues for treating this devastating abnormality.

The births of the Gaucher mice were monitored carefully. But there was a surprise: the mice born without the activity of the glucocerebrosidase enzyme looked different than the investigators anticipated, with a peculiar ridged appearance to their bodies and dry, brittle skin described by one researcher as Acellophane-like.@ These mice could not feed, had trouble breathingCand died within 12 hours after birth. As far as the researchers knew, there was no form of Gaucher disease that affected newborns so quickly and aggressively. And while some Type 2 babies have dry, scaly skin, they had nothing to compare to the cracked, paper-thin skin seen in the Gaucher mice. Still, the mouse model clearly suggested there *is* such a form of Gaucher disease. Had this variation already been seen and described, but not recognized as a form of Gaucher disease?

The researchers carefully reviewed the scientific literature, talked with neonatologists (pediatricians specializing in the first few months of life) and other doctors who worked with newborns, and continued to review the evidence of their mouse model. And a new picture began to emerge: there had indeed been human infants with the peculiar look and symptoms consistent with the mouse model. A particular point was the presence in the human babies of the same Acellophane-like@ skin seen in the Gaucher mice. And like the mice, the human babies experienced crippling disabilities immediately after birth, and quickly died.

The NIH investigators had discovered a new, heretofore unknown form of Type 2 Gaucher disease. They called this new variety Aneonatal Gaucher disease,@ and following publication of the initial findings and a follow-up study describing 14 babies with neonatal Gaucher disease, more cases are being reported with regularity. The original research team is now working with physicians and scientists from around the world to not only identify new cases but study them in greater detail.

Several pivotal points are emerging from this cooperative effort, including the fact that a second lipid (glucosylsphingosine) has been found to accumulate in the brains of neonatal Gaucher babies. This lipid is known to be toxic to the nervous system and may well account for the severity of Type 2 Gaucher symptoms. Another unexpected insight came with the Acellophane skin@ first seen in the Gaucher mice. The skin of both the Gaucher mice and human babies with neonatal Gaucher disease share significant and similar skin abnormalities, suggesting an important role for glucocerebrosidase in maintaining the integrity of the skin. Aside from expanding our basic knowledge of the skin, this discovery may serve as an accurate means of making a specific early diagnosis of both classic and neonatal Type 2 Gaucher disease.

Perhaps most importantly, it now appears that neonatal Gaucher disease is even more common than the classic Type 2 version of the disease seen in infants. In using genetic alteration in a mouse model as a technique for exploring a specific disease, researchers redefined our understanding of Gaucher disease, discovered unexpected new information about the structure and function of the body-s largest organ (the skin), and opened new and promising doors to diagnosis, treatmentBand a larger understandingBof a devastating human disease.